Scand J Work Environ Health 2009;35(3):157–161

Settling the question – the next review on shift work and heart disease in 2019

The *Scandinavian Journal of Work, Environment & Health* has published three reviews examining the epidemiological literature on the association between shift work and heart disease ten years apart – Kristensen in 1989 (1), Bøggild & Knutsson in 1999 (2) and now Frost et al in this issue (3).

Kristensen concluded that "[...] there is a positive correlation between study result and quality so that the better studies in the field consistently find a modestly higher incidence of CVD [cardiovascular disease] among shift workers [...]. The relative risk of 1.4 found by Knutsson et al is consistent with the results of other studies in the field and must, for the present, be regarded as the most reasonable estimate [p 170]" (1).

Next, Bøggild & Knutsson reviewed 17 studies and reached almost the same conclusion: "On balance [...] the most convincing study [...] leads to an overall impression that shift work is related to CVD and that shift work increases the risk by about 40%, among both men and women [p 95]" (2).

Finally in this issue, on the basis of 16 studies, Frost et al conclude that "[...] this review finds limited evidence of a causal association between shift work and ischemic heart disease [p 177]" (3).

Do the reviews disagree? The inclusion and exclusion of studies as well as different interpretations of the methodological quality might partly explain the slightly different conclusions, but there *were* differences in the evaluation. More importantly, these three reviews underlined the current situation that, in 20 years, we have not come much closer to understanding the alleged association between a relatively prevalent work environment exposure and a potential fatal consequence. This is unsatisfactory.

The next review, due in 2019, should finally be able to settle the question: Do shift workers have a higher risk of heart disease? In order to reach the objective, we do not need more of the same. The studies to be included in the coming review must be of better quality. Researchers will have to focus on the methodological problems and deal with them through better planning. The crucial problems for researchers to solve will be to choose a valid study design and, in cohort studies, to choose a relevant control group, refining exposure assessment, control selection, and controlling only the relevant confounders – albeit more of them.

What study design should be pursued? The largest methodological problem is related to exposure assessment, and a single question on whether the subject works day or shift hours is far from enough. On the other hand, although not without problem, the effect is well described and information on heart disease can be found in many registers. This suggests nested case-control studies as one possible relevant design that is not often used. The advantage of such a design is that the researcher can focus his or her resources constructing more relevant exposure information among those contracting ischemic heart disease (IHD) and a subset of healthy controls.

Researchers will have to identify factories with historical work schedule information or other hard evidence of working schedules. In Denmark, years ago workers were entitled to a tax reduction for each hour worked at night. We were initially thrilled, but unfortunately public records of historical tax information were not kept in a form enabling the identification of the proxy information on night work, so we ended up on a blind trail. It does suggest, however, that researchers should be looking at all kinds of information in order to find valid exposure data.

Most of the epidemiological studies have been on rotating shift work, some even used fixed night work as control cohorts. From a theoretical point of view there is, however, an indication that permanent night shift work is related to IHD.

Also, neither two-shift nor permanent evening shift work has been investigated in any detail. Even so, it is encompassed in the commonly used ad hoc definitions in the literature. It remains to be shown whether permanent evening or two shifts without night work is a risk factor for IHD, and whether the risk is of the same magnitude as with night work. From a theoretical point of view, it would be surprising if it were as evening work is mostly related to social problems while night work is related to physiological desynchronization of circadian rhythms.

In general, the characterization of an exposure should encompass its nature, the amount, and the time relationship (4). A thorough shift work exposure should encompass at least the following modalities (however, it should be stated that they are mostly based on theory as there are not much empirical data):

The type of shift work. Is evening or night work included? Is the schedule rotating or permanent? Does the schedule cover the whole week (ie, continuous) or only weekdays (ie, discontinuous)? Even among shift workers, spare time on weekends is more highly valued than any other time of the week, and the inclusion of weekend work would normally lead to negative social effects. It could then be anticipated that shift work including weekends would be more demanding than non-continuous work.

The schedule. The literature shows that a clockwise rotation (5), reduction in the number of consecutive night shifts in a row (6), and a more ergonomic approach to shift work scheduling (7) are leading to lower biological risk factors of IHD as cholesterol and triglycerides. But if these ergonomic criteria are of importance in diminishing the strain of the shift schedule, then a schedule following ergonomic criteria should lead to a lower risk of IHD than a schedule which does not, even when the amount of night work is the same, for example. This makes it important to incorporate some kind of formal description and comparisons of shift work schedules. Even more so, a schedule that changes in one dimension will often have changes in other modalities as well – more often probably in a negative direction. As an example, the change from a counter-clockwise to clockwise schedule leads to a better circadian rhythm, but at the same time diminishes the amount of desirable social weekend hours. One possible solution would obviously be to give the actual schedule with the start and stop hours of the shifts, and preferably indicate weekends. For future reanalysis, as much information on the shift work schedule and the dose of shift work should be included in the "material and methods" section of the publication or kept for the use of other researchers when digging into the possible effect of different schedules.

The amount of shift work per month or year. If shift work is a risk factor then the "concentration" thereof would probably be relevant. The data should probably include the number of different shift types worked (number of evening shifts, night shifts, and weekends). It would be surprising if the association were linear, so modelling should be driven by thought more than habit.

The number of years in shift work. If shift work leads to heart disease, a dose-response is likely to exist in the sense of years on shift work.

One would then have to somehow summarize this information. One possible exposure variable of interest would be an "integrated lifetime exposure", that is the sum of the products of the number of, for instance, night shift hours per month and the numbers of years worked on this particular schedule.

In population-based studies using questionnaire data, the exposed groups classified as shift workers might include, for example, evening work, night shift work with only a couple of nights a month, and permanent night shift work in continuous operations. In general, this misclassification of exposure would tend to diminish any real association between shift work and outcome.

It seems that exposure should be delimited to above a certain level, in order to have enough contrasts between shift and day work. It would be unreasonable to believe that a few months of shift work over a lifetime would raise the risk. A useful approach would be to identify and compare groups with a wide variety of schedules.

The choice of the comparison group is crucial when the impact of shift work is assessed in cohort studies. Every comparison is done with reference to a non-exposed group. In principle, the comparison group should be what the shift workers would have been, if they were not shift workers. And that is not necessarily a day worker! Shift workers tend to differ from day workers socially, economically, and in personality factors. If the comparison group differs from the exposed groups in relevant ways other than the working time arrangement, potential confounding may be present. In almost all of the literature encountered, shift workers have been compared to day workers without question. Another approach could be instead to make comparisons within shift working groups with different amounts of shift work, as these groups would tend to be more alike.

We normally try to overcome these differences in other potential risk factors for IHD by restricting or modelling our results. This should always include age, gender, social class, and relevant work environment factors that have been shown to differ between day- and night-working populations, doing the same type of job (8). The possibility to control for personality factors such as hostility should be considered. While the effects of sleep deprivation, social disruption, and stress related to shift work (9) should be given priority in order to fill the gaps in knowledge on the web of causation, they should not be incorporated in modelling. The same goes for lifestyle factors such as smoking, alcohol consumption, and exercise, as these can be regarded as both confounders and mediating variables, and at least multivariate models should be presented both with and without these factors.

This also points to the important, but neglected, influence of culture in lifestyle habits; it might well be that shift workers in some social classes or countries adapt to shift work by smoking while in others they do not. Moreover, this should be carefully addressed when designing studies.

Secondary selection bias is the traditional methodological problem described in relation to shift work research. A large proportion of shift workers leave shift work within a few years. Some leave due to management changes, for instance when a company modifies the work schedule from three- to two-shift, others leave due to changes in the social value assigned to the shift work, and a part leave due to health problems, for instance when experiencing gastrointestinal disorders or stress related to working time. It is important to obtain a complete work schedule history. The fact that the selection process is relevant has been shown in the literature where a higher risk of cardiovascular disease has been found in former shift workers (1).

A tertiary selection process suggests that people having IHD leave shift work (10). The differentiation between secondary and tertiary selection in shift work is relevant in relation to the risk of former shift workers. If the shift worker has IHD when he leaves shift work, he should be regarded as belonging to the shift work exposed group, while the secondary selection process would be in operation before clinical signs of IHD emerge. The distinction is not easy to make as, for instance, hypertension can be the first sign of IHD, and misclassification would be easy. The tertiary selection process will be a potential problem in case-referent and cross-sectional studies only. Again, it suggests that the researcher must obtain a full working time history for both cases and controls, and examine ways of computing the risks.

There has been less focus on the primary selection into shift work. People choose to apply for a shift work job with some kind of anticipation of whether it will suit them or not. This judgement can be based upon former experience or solely on self judgement of, for instance, social possibilities or sleep habits. A few studies have suggested that self judgement is relevant, probably based on sleep habits. The literature has shown there is a relation between the feeling of having chosen shift work and better adjustment to shift work, but it has not been shown whether this feeling of self-selection influences biomarker levels or the risk of IHD.

Some applicants apply for a shift working job as they see it as their only chance of getting a job. In some instances, day work is used as a reward for some years of shift work (when only internal applications are considered), forcing new applicants into shift work in order to obtain a daytime job at a later time. In these situations, the so-called "voluntary" application could be a choice between shift work and

no work at all. The situation in the labour market might thus influence both the primary and secondary selection processes. In other words, it is not a random sample of people that end up doing shift work (11); this also points to the need for a thoroughly selected comparison group.

Researchers should not control for all differences. One problem in the examined literature is the apparent confusion over mediating variables and confounders. In many of the reviewed articles, researchers have controlled for every difference found between the groups. Traditionally, the question has been posed: Are shift workers "born or made [p 5]" (12)? That is, were the differences present before starting the job or are the differences a result of the shift work experience. In the first instance, controlling for differences should be made; in the second, it may be more appropriate to see the differences as an effect of shift work.

A confounder is defined as a factor that meets all of the following three conditions; it is: (i) a risk factor for heart disease, (ii) associated with shift work status in the source population (ie, the population at risk from which the cases are derived), and (iii) not affected by the exposure or disease (13). A mediating variable, on the other hand, is an intermediate step in the causal path between exposure and disease.

As an example, some studies have controlled for differences in blood pressure between shift and day workers (2). High blood pressure is a risk factor for IHD and is associated with shift work status in some studies. However, it might be affected by the exposure in this way being a potential link between shift work and IHD, with blood pressure being higher *because* of shift work, and thus not fulfilling condition number three. When controlling in the study design by restricting to use only normotensives or adjusting in multivariate regression analyses, the effect will normally be an artificially lower risk than is really present, except when confounders are non-differentially misclassified. In that case, bias can be in either direction. Smoking, high body mass index, and differences in lipids like cholesterol can likewise be regarded as an effect of being a shift worker

Is it all due to a possible effect of stress in shift work? Shift workers can be exposed to stress as a part of psychosocial work conditions, for example as described in the models by Karasek or Siegrist (14). But this is related to the content of work, not shift work; if differences in this type of stress are present between day and night shift workers, then it might be best regarded as a confounder. Stress could, on the other hand, also be a result of the working time schedule and its impact on family life conditions and, in that case, a possible explanation of the association. If stress, in the Lazarus sense (15) (taking account also of the individual's appraisal), is involved in the causal pathway from shift work to heart disease, shift work might only be a risk for certain people. Some workers do not regard their shift work as being particularly problematic; they sleep well, are comfortable with their working hours, and would not want it any other way. This point has been used to propose that shift work should be reserved for those who choose it themselves. It might be that if shift work were not perceived as stressful, then the risk of IHD would not be higher for shift workers. It might explain the heterogeneity of the epidemiological literature. But again, that has not been documented.

Shift work could also be a risk factor only when interacting with other known risk factors, having superadditive effects on traditional risk factors such as body mass index and smoking (16). This is also worth examining.

Having raised all these methodological problems in research on shift work, is it worth using time and resources to examine it? We must! The literature has suggested an association, but 20 years of studies have not given a clear answer. We are curious, but most of all we need to be able to answer the question in order to give information to the shift working population. Then, if we find that the risk is present, we have to examine ways to reduce it.

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