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Shift work and cardiovascular disease

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ÅKERSTEDT T, KNUTSSON A, ALFREDSSON L, THEORELL T. Shift work and cardiovascular disease. *Scand J Work Environ Health* 10 (1984) 409—414. This paper reviews a number of studies which have presented results on the association between shift work and cardiovascular disease. It is suggested that many of the early studies suffer from methodological flaws which render them difficult to interpret. In studies in which incidence of disease has been computed and related to exposure to shift work, the results indicate a higher risk for cardiovascular disease among shift workers as compared to day workers. The evidence cannot yet, however, be considered conclusive.

Key terms: epidemiology, morbidity, mortality.

There seems to exist a widespread consensus that shift work causes disordered sleep and gastrointestinal disease. [For reviews see Åkerstedt (1), Harrington (10), Menzel (15), Rutenfranz et al (20), & Thiis-Evensen (25).] Cardiovascular disease (CVD) does not seem to be affected. Yet, some recent research has begun to suggest that there still might be a connection between shift work and CVD. In addition, there seems to be methodological reasons to reevaluate some of the earlier studies. The present paper will attempt to review briefly some of the major postwar studies on this topic, including some very recent unpublished data. First, however, we will introduce some background information on shift work.

Shift work

The term "shift work" is vague but usually refers to a workhour system in which a relay of employees extends the period of production beyond the conventional daytime third of the 24-h cycle. The particular varieties of shift work may then differ greatly with respect to the permanency of the workhours, the completeness of the 24-h coverage, or the regularity in the alternation between shifts. A tentative classification may yield, aside from day work, permanently displaced workhours (ie, either morning, evening, or night work), rotating shift work (alternation between thirds of the 24-h cycle), roster work (less regular than the former), and unscheduled workhours (work when "needed" — often self-employed individuals).

Since the major difficulty in shift work seems to concern the night shift, we will, in the following review, concentrate on those schedules that contain such shifts, ie, conventional three-shift work (1.6 %), roster work with night shifts (3.5 %), and permanent night work (0.5 %). For simplicity, we will refer to these as "shift work." The figures within parentheses have been obtained from a recent national survey of workhours in Sweden (21). (Permanent day work comprises 70.7 %, permanent morning or evening work 7.1 %, two-shift or day-oriented roster work 9.3 %, and unscheduled workhours 7.0 %.) Most studies of health in relation to workhours have concerned rotating three-shift work.

Direct effects of shift work

The development of CVD disease is a slow process with a multifactorial etiology (8). Before considering studies of disease and shift work, we will, therefore, summarize the more direct and immediate impacts of shift work.

One of the major effects of shift work is the interference of workhours with various social activities. [For reviews see Fröberg (9) & Wedderburn (29).] Thus the direct time conflict will reduce the amount of time available to spend with family and friends or in various forms of recreation or voluntary activities. In addition, the alternation pattern of workhours and their anticipated interference may make participation in regular activities less worthwhile, resulting in passivity. Friends might also find the availability schedule of a shift worker too complicated and therefore refrain from contacts. The result is often social isolation and a reduced capacity to fulfill the various social roles expected by society (17).

Another obvious effect of shift work on well-being is the shortened sleep (2—3 h) and increased fatigue

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connected with night work (3). This problem is, apparently, due to the effects of circadian rhythmicity. Night work exposes the worker to the circadian trough of physiological and psychological activation, whereas day sleep is disturbed by the daytime circadian upswing of physiological activation. Apparently, also appetite and digestion are affected by similar mechanisms (20).

As may be expected, also the circadian pattern itself is disturbed by shift work (4). This disturbance looks like the initial adjustment to a new activity phase, but the adjustment is never completed. The result is a disordered circadian system for the duration of the night shift period. For cardiovascular variables such as heart rate or blood pressure, the normal 24-h pattern is considerably flattened (15). The same occurs for (urinary) noradrenaline but to a much less extent for adrenaline (2). In an experimental study of day workers who were suddenly rescheduled to temporary night work, we found increases in urinary adrenaline excretion, serum cholesterol, glucose, uric acid, and potassium (24). The levels fell on return to day work. In a cross-sectional study we have found higher levels of lipids, blood pressure, and smoking among shift workers (12). Similar results have been obtained in two other studies (19, 23).

Apparently then, shift work has several effects that might be related to CVD.

Shift work and epidemiologic methodology

A major methodological concern in occupational epidemiology is to obtain reliable and valid information on exposure and response in the population (11). In the present context particularly the former is subjected to confounding, partly due to various selection processes.

Selection *into* shift work may operate through formal company selection procedures or simply through the worker's estimate of his own ability to withstand irregular living. Presumably this selection might lead to shift workers being healthier than day workers at the outset. This presumption is speculative, however, and the extent of this selection is unknown.

Selection *out of* shift work is observable in all studies in which work schedule history has been obtained, but Thiis-Evensen (26) has paid special attention to this phenomenon and showed that out of 2 137 workers with at least one year of exposure to shift work one-fourth had been transferred to day work within 10 years. Forty-two percent had medical reasons for leaving — mainly gastrointestinal, nervous, or circulatory disease. A shift working group will thus, on the whole, constitute a positive selection and contain a bias towards better health. A day working group will contain the opposite bias, and many individuals in that group will have had considerable exposure to shift work.

The selection processes make cross-sectional prevalence studies difficult to interpret, particularly for diseases which develop over long periods of exposure time (11), like CVD. The preferred method would rather employ cohort techniques with incidence (new cases only) measures related to the amount of exposure (yielding incidence rate).

Another selection problem concerns the comparability of work tasks in exposed and nonexposed groups. Often, eg, day work involves maintenance tasks instead of routine production tasks. This difference may mean different work loads, as well as different socioeconomic status, both of which may be associated with morbidity.

The success in handling confounding factors will be a major criterion in the evaluation of the existing epidemiologic studies of shift work.

Studies of prevalence and cumulated incidence

The most frequently cited study on shift work and CVD (and other diseases) is that of Aanonsen (5). He made five annual routine medical examinations of 1 106 three-shift workers at a group of electrochemical plants in Norway, and he included only those individuals who had been employed from the start (1948) and remained throughout the five years. The cumulative five-year incidence for angina pectoris and myocardial infarction was clearly lowest for the shift workers (1.1 %) when compared to the day workers (includes two-shift) (2.6 %). In the group that had changed from shift to day work for medical reasons, the frequency was even lower (0.8 %). (The latter workers had changed because of either disturbed sleep or disturbed digestion.) The highest prevalence, however, was found among those exshift workers who had been transferred to day work for other than health reasons (3.2 %). No direct comparison was made of the four groups. Interestingly, in a separate retrospective study (12 years) of subjects aged 51 years or more, absence due to CVD was highest among the nonmedical transferees (137 d/100 person-years). Shift workers had 23 d, whereas day workers had 21 and medical transferees 10. Yet it was concluded that shift work was not related to CVD.

The preceding conclusion seems untenable for several reasons. First, the total pattern across the four groups was not considered — in spite of the fact that the nonmedical transferees had an incidence three times that of those remaining in shift work. Second, the shift workers were younger and had fewer occupational skills. Third, the amount of exposure to shift work was not considered. Fourth, and most important, those who left the cohort (through death, disease, retirement, or other reasons) during the period of observation were excluded from the analysis. This group of dropouts from the system may well have had a high incidence of CVD (and other disease) and is clearly a group of major interest when the health effects of shift work are being investigated.

Another major study is that of Thiis-Evensen (26). He used company health files covering 30 years to select a group that had left work because of death or retirement (N = 1 390). He found that CVD was a dominant cause of death, particularly among shift workers. In addition the proportion of invalid pensions due to CVD (relative to other causes) was higher among shift workers. The author attributed these results to the slightly higher age of the shift workers. In any case, the meaning of the difference in the distribution of causes is unclear since the number of subjects originally exposed was not considered when the proportions were computed, let alone the *amount* of exposure. There were also differences in work tasks and personnel turnover between the groups.

In an additional study Thiis-Evensen (26) calculated the morbidity in CVD in the years following the prior retrospective study. He found no difference between the workhour groups with respect to morbidity, but a higher number of sick days due to CVD for day workers. As with the study by Aanonsen, interpretation of the results is made difficult because of preselection, untraced dropouts, lack of consideration of the amounts of exposure, and age and task differences between the groups. These original studies were later extended (27) without essentially affecting the main conclusions.

Among the early studies finding a higher incidence of myocardial infarction among shift workers is that of Pierach (18). The methodology was not, however, described in any detail, and conclusions are therefore difficult to draw.

Koller & co-workers (14) investigated 270 workers at an Austrian oil refinery. They found a higher prevalence of cardiovascular symptoms and complaints among the three-shift workers. This material was followed-up and extended five years later (13) with medical examinations and interviews. The day and shift workers were also matched with respect to age and experience. The results showed that the highest morbidity for diseases of the circulatory system was found among shift workers (20 %). Day workers had 7 %, and exshift workers 15 %. (The difference increased with exposure.) Once again, however, the weaknesses are the prevalence data, possible preselection, and different job characteristics. Yet, control of dropouts and the inclusion of age and exposure controls make the study valuable.

In a rather unusual approach Michel-Briand & co-workers (16) made a clinical examination of 200 recently retired workers (normal age criterion). They found an excess prevalence of angina pectoris in transferred shift workers — 29 % against 12 % for permanent shift workers and 8 % for day workers. For hypertension the figures were 33, 25, and 10 %, respectively. Even more than in the preceding studies, however, prior selection constituted a major problem since the number of workers lost through CVD would be very high in this age group.

The studies described in this section do not allow any firm conclusions. There are several reasons for this, but the most prominent one is clearly the failure to account reliably for the entire population that has been exposed to shift work.

Studies of incidence rate

The largest study of incidence rate is that of Taylor & Pocock (22), who used health statistics from 10 companies (N = 8 700) to compute the incidence of CVD in a cohort followed over 12 years, starting in 1956. Practically all the original cohort members were traced. National statistics were used to compute "expected" age-corrected incidence figures. The standardized mortality ratios (SMR) [derived from the tables of the original report (22) by the present authors] for all cardiovascular diagnoses taken together were 92 for day workers, 102 for shift workers, and 133 for exshift workers. None of these values were statistically significantly different from 100 (ie, the national reference). For atherosclerotic heart disease the corresponding values were 94, 103, and 125 (none significant). For hypertension the corresponding values were 74, 130, and 208 (none significant). The trends towards higher ratios for shift workers than for day workers were not statistically significant. The exshift workers, who had the highest ratios, do not seem to have been included in the statistical testing or in the overall analysis.

In a cohort study by Angersbach & co-workers (7) a slight but nonsignificant excess of CVD morbidity was also found among shift workers (N = 640). The cumulative incidence in an 11-year cohort was 14.8 % for the day workers and 16.8 % for the shift workers. In a third group, apparently not included in the statistical testing, those who were to transfer eventually to day work had an approximate incidence rate of 0.025 cases per person-year before transfer [estimated by the present authors from figure 3 of the original report (7)]. After the transfer this rate increased to 0.06. The corresponding figure for the permanent shift workers was 0.0175 and that for the permanent day workers was 0.015. Yet, apparently considering only the comparison between permanent day and night workers, the authors concluded that there was no relation between shift work and CVD. Interestingly a third of the original cohort members were lost through retirement, death, or withdrawal from the company for other reasons. This group may have had a major effect on the incidence rate figures.

In a recent study which is still being analyzed (Knutsson et al), we have collected the ischemic heart disease incidence in a paper industry between 1968 and 1983 for a cohort of 504 shift and day workers and related it to the amount of exposure to shift work. (Those who had less exposure than three years or who had left shift work more than 10 years ago were removed.) Few original cohort members were untraceable. The resulting standardized risk ratio for shift work against zero years of exposure reached 1.6. The risk for workers with one to two years of exposure was not possible to establish (no cases occurred). In the three- to five-year exposure group the risk was 2.6, for 6—10 years it was 2.7, and for the 11- to 15-year and 16- to 20-year groups it was 2.3 and 2.6, respectively. But in the ≥ 21-year group the risk fell to 0.4. The latter might possibly be construed as a selection effect.

The studies described in the present section have the advantage of using incidence data adjusted for the amount of exposure. Exits from the cohort also seem to be accounted for. Taken together, the three studies suggest that shift work may possibly be associated with a higher risk of falling ill due to CVD. Yet two factors remain unaccounted for — job differences and precohort selection. The effect of the first is unknown, and that of the latter may be better health prospects for shift workers when the cohort is formed. The latter may lead to an underestimation of an association between shift work and CVD.

An approach with aggregated data

A different approach from those discussed has been taken by Alfredsson & co-workers (6). In a first step an assessment of how common certain work conditions are in different occupations was made by means of an interview survey (N = 14 500) performed by the Swedish Central Bureau of Statistics. For each characteristic the occupations (271) were ranked according to the percentage of employees reporting the characteristic. An occupation was then classified as strenuous (high exposure) or nonstrenuous (low exposure) due to its position over or under the median, respectively.

This aggregated information on occupations was then used in a case-referent study. All male cases of myocardial infarction in 1974—1976 in a Stockholm area were selected (334). These cases were age-matched against referents from the same area of residence, yielding 1 216 subjects. Each individual was then, according to his occupational code, assigned an exposure status for different work characteristics, such as the presence of shift work, the degree of monotony, unemployment risk, overtime, piece work, hectic work, influence on workpace, heavy lifting, vibration, and many others. The relative risk for men in high-exposure occupations developing myocardial infarction compared with other working men was then calculated.

The analysis showed that only two work-environment factors were significantly related to myocardial infarction incidence. The first was exposure to monotony [rate ratio (RR) = 1.32, $p < 0.02$] and the second was shift work (RR = 1.26, $p < 0.04$). (For comparison, smoking obtained an RR of 1.28, $p < 0.03$.) Several attempts to study confounding factors were made, and the statistically significant shift work ratio was removed by smoking.

In another study which is still being analyzed, we have used the same method with aggregated information on occupations in a cohort study. The study population (N = 958 096) was defined as persons with an occupational code in the census, aged 20—64 years, and living in a specific area. The central hospitalization register provided information on all inpatient care of the study population for a period of one year. Again the occupational code was used to classify each individual as belonging to the high- or low-exposure group. For each job characteristic the standardized morbidity (hospitalization) ratio was calculated as the percentage of observed cases in the high-exposure group in relation to the number of expected cases. The basis for the calculation of expected cases was the relative number of cases in the low-exposure group.

Among the 958 096 people 2 530 diagnoses of ischemic heart disease (International Classification of Disease 410-414) occurred. For males the highest ranking (single) work-environment predictor was shift work with a standardized mortality ratio of 119. Four other job characteristics also reached statistical significance (one of them was monotony). Among females shift work ranked second after "no influence on work breaks" (SMR = 140). Fourteen other job characteristics reached statistical significance. The association remained statistically significant also after adjustment for a number of potential confounding factors, such as smoking, income, marital status, area of residence, type of community, full-/part-time work, amount of heavy lifting, etc.

"Exposure" to shift work did *not* have a statistically significant association with incidence of hospitalization for other causes such as cerebrovascular disease, psychiatric disease, suicide, alcoholism, cancer, gastrointestinal disease, or diabetes. For accidents and low-back pain there were significant associations for both sexes with "exposure" to shift work. The results suggest that shift work is rather specifically related to ischemic heart disease.

Both aggregated studies suggest that shift work is in some way associated with risk of ischemic heart disease. It should be mentioned, however, that the aggregated method precludes consideration of the *amount* of exposure. On the other hand the method probably retains the transferees (to day work) as shift workers since the transferees are likely to stay in their old (shift work) occupational category despite their day work.

Another trait of the aggregated technique is that it contrasts occupations instead of individuals in an occupation. This procedure may increase the amount of confounding from other work-environment variables. On the other hand it gives access to large stores of data with possibilities to control for other job characteristics without individual self-report biases. Possibly aggregated techniques might be a complement to conventional cohort studies.

Summary and discussion

Of the studies discussed most suggest a relation between CVD and shift work. Those two which point in the opposite direction did not properly consider the whole population of exposed individuals, nor did they attempt any differentiation of morbidity with respect to the amount of exposure. In those studies in which such considerations were made, the results suggest, albeit weakly, that shift work may be related to CVD. Such a connection could be hypothesized to occur directly through the neuroendocrine system due to the load imposed by irregular life. It might, however, equally well be due to health-related behavior (eating, smoking, etc), or it might even be the case that shift work is merely a common denominator for various negative job characteristics that happen to occur together with shift work.

Still, none of the studies discussed has supplied *indisputable* evidence that shift work plays a role in the development of CVD — in particular, differences in job contents and precohort selection processes have not been accounted for. Taken together, however, there seems to be enough evidence to justify a renewed major effort to produce conclusive evidence.

Such a study would have to be a long-term cohort investigation starting at recruitment, preferably with a prospective design requiring close monitoring of exposure. To avoid a dilution of the results from too rapid a turnover of personnel (with resulting low exposure for much of the cohort) worksites with few possibilities for transfer should be selected. Furthermore, the analyses should be made separately for different exposure levels to allow for nonlinearity. The selection into shift work may be difficult to control for. Possibly this control could be handled through the selection of worksites with no alternative job opportunities. The problem with task differences, finally, could be resolved possibly by focusing on occupations in which work conditions are homogeneous across work schedules, eg, computer programming.

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