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Key terms: cardiovascular disease epidemiology; review; risk factor; work schedule

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Shift work, risk factors and cardiovascular disease

by Henrik Bøggild, MD, Anders Knutsson, PhD,

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The literature on shift work, morbidity and mortality from cardiovascular disease, and changes in traditional risk factors is reviewed. Seventeen studies have dealt with shift work and cardiovascular disease risk. On balance, shift workers were found to have a 40% increase in risk. Causal mechanisms of this risk via known cardiovascular risk factors, in relation to circadian rhythms, disturbed sociotemporal patterns, social support, stress, behavior (smoking, diet, alcohol, exercise), and biochemical changes (cholesterol, triglycerides, etc) are discussed. The risk is probably multifactorial, but the literature has focused on the behavior of shift workers and has neglected other possible causal connections. In most studies methodological problems are present; these problems are related to selection bias, exposure classification, outcome classification, and the appropriateness of comparison groups. Suggestions for the direction of future research on this topic are proposed.

Key terms cardiovascular disease epidemiology, review, risk factors, work schedule.

Cardiovascular diseases (CVD) are the leading cause of death and disability in most industrialized countries. Medication, operations, and other tertiary preventive actions may have changed the lethality of CVD (1), but rational primary prevention should aim at the causes of CVD and thus reduce the incidence.

The causes of CVD are multifactorial, and during the past 10 years it has been realized that also conditions in the work environment contribute to the etiology of CVD (2, 3). A variety of chemical substances has been identified, notably, carbon disulfide and nitroglycerine, but also lead, cobalt, arsenic, solvents, and organophosphates, as causing CVD. The impact of these factors on public health is limited, however, as regards the number of people exposed. More important, from the point of view of society (4), are the psychosocial factors sedentary work, monotonous and other stressful work conditions, passive smoking, and shift work, which have also been identified as occupational risk factors (2). Examining Danish prevalence figures and risk ratios for known chemical and psychosocial factors, Olsen & Kristensen (5) found the etiologic fraction (the amount of disease that would be prevented if the cause was not present) for psychosocial

factors to be around 20% (sedentary work excluded, as it can be counteracted during leisure time). Dealing with risk factors in the workplace would therefore have a potentially large effect on the prevalence of CVD.

There is no agreement on a definition of shift work in the literature, but it often encompasses work outside the conventional day time and thereby covers fixed evening and night work, roster work, and ordinary 3-shift work. The number of employees working shifts seems to be growing, mainly due to the demand for service around the clock. In Europe approximately 18% of the work force works at least 25% of the time at night, and an even larger portion works outside normal workhours (6), a figure consistent with estimates from other industrial countries (7). This characteristic makes shift work one of the most widespread work environment risk factors for CVD.

Knowledge of the links between shift work and CVD are particularly valuable, as shiftwork problems can only be prevented by manipulating these links, not by eliminating the primary exposure, as it is necessary to have a part of the labor force working outside normal workhours due to technical, economic or public service obligations. In contrast to this situation, chemical substances can very

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often be substituted by less cardiotoxic substances, and high-strain jobs can be changed to lower strain jobs by rearranging the way the work is organized.

This article attempts to elucidate the links between shift work and CVD in order to identify possible points of prevention, first by establishing the evidence of the postulated relationship, then by discussing the routes by which a relation could be transferred, and finally by suggesting future direction for research.

Methods

The literature was searched in MEDLINE and NIOSH-TIC with key words and MESH headings related to shift work, work schedules, cardiovascular risk factors, and cardiovascular disease. The reference lists in published papers were examined and additional studies reviewed. Conference reports from ICOH (International Commission on Occupational Health) scientific committees on shift and night work and on cardiology in occupational health were read. Eventually researchers in the field were contacted.

Studies were included if they were in English or Scandinavian, if they compared shift and day workers or followed shift workers after a change of schedule, and if cardiovascular risk factors or actual CVD end points were reported.

All the studies were judged for methodological quality according to the principles of Kristensen (2) with the time dimension of the study, control of confounders and selection, measures of exposure and outcome, and general design and statistical analysis being taken into account.

Results

Assessment of the evidence

The search identified 17 studies on CVD end points in shift workers. Half of these studies had been evaluated by Kristensen in 1989 in the hitherto most comprehensive review (2). On the basis of methodological quality, Kristensen had 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. . . [p 170]" and regarded the relative risk of 1.4 found by Knutsson et al (8) to be the most reasonable estimate. The review was updated in 1993 (9), essentially by including 1 additional study, and the conclusion was the same. The literature has also been reviewed by Åkerstedt et al (10), Orth-Gomér (11), and Wagner (12), whose conclusions have been similar.

The 17 studies are listed in table 1, and the most reasonable estimate for each of the studies has been derived for figure 1. The cross-sectional investigations and a few of the cohort studies reported prevalence figures, and, on the basis of these, odds ratios have been calculated. For the study by Tüchsen (14), we pooled information on all types of shift work and calculated 95% confidence intervals (95% CI) for comparison. As most studies report several risk estimates, assumptions have been made in the selection of estimates for the figure. We have selected the ones that were most reasonable from the point of view that adjustments for confounding factors such as age, gender, nationality, region, other job functions, and social class should be made, while adjustments for cholesterol, smoking, social support, and the like should not be since they are considered mediating factors, combining shift work and CVD, rather than potential confounding factors. We have discussed this view in more detail later in this report. We had to make a compromise in this respect since this distinction was not made in the studies that report either crude estimates or estimates adjusted for all variables that could be regarded as confounders.

Figure 1 shows that the 17 studies lead to very different risk estimates, from an odds ratio of 0.4 to an odds ratio of 3.6. Within these outliers the risk estimates span from 1 to 2. Most of the large studies report a risk estimate around 1.4 (8, 15–18). On the other hand 4 large studies (19–22) failed to find an association, although of roughly the same methodological quality. The figure gives the impression of heterogenic studies (discussed later).

Four investigations attempted to study a dose-response pattern. Knutsson et al (8) found a steep, almost linear increase to 20 years of shift work, for which the relative risk was 2.8. Kawachi et al (17) also found risk to increase, although not in the same magnitude. Tenkanen et al (18) found a weak and statistically insignificant dose-response. Finally, McNamee et al (19) found no dose-response pattern.

Until menopause, women have a lower risk of attracting CVD. This difference can partly be explained by hormonal differences (estrogens) and by differences in lifestyle (23). There are no indications that women should be "immune" to the consequences of shift work (24). The risks of women have been dealt with in the study by Alfredsson et al (25), in which women working in occupations with a large proportion of nondaytime work had an elevated standardized mortality ratio (SMR) of 152 (95% CI 119–191), by Knutsson et al (15), who found an odds ratio of 1.7, and by Kawachi et al (17), who found a relative risk of 1.3 for American nurses. These figures suggest that women have the same risk as men.

As the development of CVD is slow, it would not be suspected that disease would show within a few years of the start of shift work. The study by Knutsson et al (8)

Table 1. Epidemiologic studies in relation to shift work and morbidity and mortality from cardiovascular disease (CVD) (ex-shift workers not included). (PR = prevalence rate, OR = odds ratio, 95% CI = 95% confidence interval, AMI = acute myocardial infarction, SMR = standardized mortality ratio, RR = relative risk, ICD = International Classification of Diseases, WHO = World Health Organization, SHR = standardized hospitalization ratio, DM = diabetes mellitus, BMI = body mass index)

Reference ^a	Population ^b	Exposure / referents	Disease	Controlled confounders	Main results ^c
<i>Cross-sectional studies</i>					
Thiis-Evensen, 1949 (106) (xx)	1390, of which 1/3 shift workers, 388 cases	3-shift / day work same factory	Mortality, CVD?	.	PR 34% shift work, 25% day work; <i>OR 1.55 (95% CI 1.21—1.97)</i>
Aanonsen, 1964 (13) (xx)	Men, 380 shift workers, 345 day workers, 13 cases	Continuous shift work / day work	Morbidity, angina pectoris and AMI	Age	PR: 1.1 % shift work, 2.6% day work; <i>OR_{AMI} 0.43 (95% CI 0.11—1.59)</i>
Michel-Briand, 1981 (61) (x)	Men, retired, 99 shift workers, 93 day workers, 19 cases	Shift work ? / day work	Morbidity, angina pectoris	.	PR: 12.12% shift work, 7.56 % day work; <i>OR 1.69 (95% CI 0.64—4.51)</i>
Koller, 1983 (26) (xxx)	Men, blue collar, 199 shift workers, 68 day workers; about 45 cases	Rapidly rotating 3-shift / day work same factory	Morbidity, ICD 390—459 (CVD including varicosis, hypotension)	Age, seniority, work-conditions?	PR: 19.9 % shift work, 7.4 % day work; <i>OR_{unadj} 3.17 (95% CI 1.2—8.4)</i>
<i>Case-referent studies</i>					
Alfredsson, 1982 (100) 1974—1976 (xxx)	Men, <65 years, 334 cases, 882 referents	Aggregated, rotating shift (changing day and night) / day (?)	Morbidity and mortality, AMI (ICD 410.00—410.99)	Age, region, smoking (aggregated)	OR 1.25 (95% CI 0.97—1.62)
McNamee, 1996 (19) (xxx) 1950—1992	Nested case-referent, among men, <50 years; 467 cases, 467 referents	1 month 3-shift / day work same factory	Morbidity and mortality, AMI	Age, weight, height, smoking, blood pressure, job status (skilled, semi-unskilled)	OR 0.9 (95% CI 0.68—1.21); no dose-response
Steenland, 1996 (20) (xx)	Nested case-referent, among men, 163 cases, 781 referents	Prevalent night shift / current day shift	Mortality CVD (ICD 410—414)	Age, race, plant	OR _{adj} 0.64 (95% CI 0.28—1.47)
Knutsson, 1998 (15) (xxx) 1992—1994	Men: 1417 cases, 1808 referents; women: 589 cases, 834 referents	Shift or night work last 5 years / day work	Morbidity and mortality, AMI	Age, tobacco, job strain, education, region	OR _{adj} men: 1.3 (95% CI 1.1—1.6); women: 1.3 (95% CI 0.9—1.8)
<i>Cohort studies</i>					
Taylor, 1972 (21) (xx) 1956—1968	Men, >52 years, 4188 shift workers, 3860 day workers, 540 cases	>10 years shift work in 10 factories / >10 years of day-work (less than 1/2 year of shift work), compared to population	Mortality, AMI (ICD 400—468)	Age	SMR 102 shift work, 92 day work; <i>RR_{unadj} 1.00 (95% CI 0.84—1.18)</i>
Angersbach 1980 (107) (xx) 1966—1977	370 shift workers, 270 day workers, 102 cases	>1/2 year continuous 12-hour rotating shift work / >1/2 year of noncontinuous day work	Morbidity, AMI, arrhythmia, hypertension etc (from sick leaves)	.	Incidence 16.8 % shift work, 14.8 % day work; <i>RR 1.13 (95% CI 0.79—1.63)</i>
Alfredsson, 1985 (25) (xxx) 1976	Men and women, 20—64 years, 985096, 1201 cases	Aggregated (other than daytime) / day time	Morbidity, AMI (ICD 410—410.99)	Age	SMR men: 115 (95% CI 104—126); women: 152 (95% CI 119—191)
Knutsson, 1986 (8) (xxxx) 1968—1983	Men, >20 years, 394 shift workers, 110 day workers, 43 cases	>6-month rotating 3-shift (process operators) / day work (maintenance) at same factory	Morbidity and mortality, angina pectoris and AMI (WHO criteria)	Age, tobacco, family status	RR 1.4 (95% CI 0.7—2.7), dose-response for work exposure 2—20 years; <i>OR_{adj} 1.53 (95% CI 0.65—3.64)</i>
Åkerstedt, 1987 (16) (xxx) 1976	Men, 20—64 years, 1059 cases	Aggregated (including night) / day	Morbidity, AMI (ICD 410—410.99), ischemic heart disease (ICD 410—414)	Age, work conditions, cohabitation, children, region, nationality	SMR AMI: 148 (95% CI 112—191); ischemic heart disease: 128 (95% CI 103—158)
Tüchsen, 1993 (14) (xxx) 1981	Men, 20—59 years, 1 293 888, 5966 cases	Aggregated (night and morning, late evening, 24-hour work, other irregular) / day work	Morbidity, ischemic heart disease (ICD8 410—414)	Age	SHR, group 1: 193 (90% CI 158—236), group 2: 215 (90% CI 192—240, group 3: 168 (90% CI 151—185), group 4: 172 (90% CI 166—182); overall <i>SHR 178 (95% CI 170—186)</i>
Kawachi, 1995 (17) (xxx) 1988—1992	Female nurses, 42—67 years, 46 956 shift workers, 32 153 day workers, 292 cases	>1 year of > 3 nights a month (rotating) / day (including fixed evening and night?)	Morbidity and mortality, AMI	Age, smoking, hypertension, DM, hypercholesterolemia, use of post-menopausal hormones, alcohol, physical activity, genetics, use of aspirin and vitamin E, male education	RR 1.31 (95% CI 1.02—1.68), dose-response
Tenkanen, 1997 (18), 1987—1993 (xxx)	Men, 40—55 years, 564 shift workers, 511 day workers, ? cases	Prevalent, mainly continuous, slowly rotating 3-shift in 5 industrial companies / day	Morbidity and mortality, ischemic heart disease (ICD9 410—414)	Age, smoking, BMI, spare-time physical activity, alcohol, blood pressure, lipid, job strain; restricted to blue collar, certain occupations	RR 1.33 (95% CI 0.89—1.99), "weak dose-response"
Bøggild, 1998 (22) 1971—1993 (xxx)	Men, 40—59 years, 1123 shift workers, 4084 day workers, 1006 cases	Prevalent work on shift or irregular work hours in 14 companies/ day work	Morbidity and mortality, ischemic heart disease (ICD8 410—414)	Age, social class, sleep, smoking, weight, height, fitness value	RR 0.9 (95% CI 0.7—1.1)

^a Overall quality of study, based on Kristensen (2) also given (range from x to xxxx), as well as the period of registration where available.

^b Gender, age, number [exposed, unexposed, cases (cohort) or cases and referents (case-referent)].

^c Selected results; reanalyzed figures in italics.

Figure 1. Epidemiologic studies on the relation between shift work and cardiovascular diseases (CVD) among men — selected estimates. (See the text and table 7.) (* indicates reanalyzed materials)

found the risk to increase after 2 years of shift work, but they did not include information on lag time, although they argued that no differences were seen with different lag time spans. McNamee et al (19) have also analyzed data with different lag times and found no differences. Likewise it could be expected that leaving shift work would lower the risk of CVD in subsequent years and eventually lead to a risk resembling that of unexposed populations, as has been shown in the case of smoking cessation. Several studies on ex-shift workers have been carried out (21, 26), but none of them have examined the effect of prolonged exposure-free periods on the subsequent risk.

The diversity of studies renders a meta-analysis problematic, but the most reasonable risk estimate seems still to be the relative risk of 1.4 derived from the hitherto methodologically most convincing study by Knutsson et al (8), whose results are supported by the demonstration of a dose-response and an equal risk for both genders.

Causal mechanisms

The next section examines the possible biological pathways linking shift work with CVD. The term risk factor is, in general, used to designate factors that link the environment to CVD and that precede disease, predict disease strongly and are dose-related from study to study independently of other contributors (27). Thus far, more than 250 risk indicators have been identified (28); however in this article we have dealt with only a minority of them and have focused on changeable factors (smoking, dieting, social support) rather than on inherent ones (age, gender, familial hypercholesterolemia, a genetic disease) (29). Furthermore, we have divided the risk factors into external risk factors and biomarkers that designate the body response to external risk factors.

The following section of the article is based on a model originally proposed by Knutsson (30). It

identifies 3 different, but interrelated pathways that lead from shift work to disease — mismatch of circadian rhythms, social disruption and behavioral changes. A 4th pathway not originally in the model consists of changes in biomarkers. The model is used as a mental aid in discussions of the potential influence of traditionally accepted risk factors.

Mismatch between circadian rhythms and sleep

Shift work leads to changes in circadian rhythms of the body and thus causes an imbalance in the homeostasis of the body that leads to internal desynchronization, the mismatch of related circadian rhythms. A mismatch of circadian rhythms may be of importance to nutrition, as both enzymatic activity and stomach emptying are circadian rhythmic and may be desynchronized from the meals of shift workers. One study found that cholesterol correlated with the distribution of meals and that cholesterol levels were higher when a larger proportion of the diet was ingested at night (31). Shift workers often change the distribution of their food intake, and, therefore, changes can occur in the concentrations of their biomarkers.

The mismatch of rhythms is known also to be important in relation to the manifestation of disease. Several studies have confirmed the well-known clinical experience that the onset of both myocardial infarction and angina pectoris is more common in the early morning. This chronobiological rhythm has been explained by a mismatch between oxygen supply and demand at awakening. The mismatch may give rise to a precipitation of myocardial infarction in vulnerable persons if the circadian rhythm of oxygen supply does not adjust promptly to the changed demand of night work. There are no studies looking at the hourly distribution of myocardial infarction among shift workers, but a peak on Mondays for the working population as a whole suggests that rising for

work is a risk factor (32), and a secondary peak in the late afternoon has been proposed to stem from a person's waking from their day sleep (33).

An increased number of ventricular extrasystoles in people who work nights has likewise been explained by desynchronized rhythms (34).

Shift workers are known to sleep less than day workers and to be more fatigued (35). There is limited knowledge on a possible relationship between lack of sleep and CVD. Sleep apnea syndrome is a risk factor for CVD (36), but no studies have looked at the relationship between shift work and sleep apnea syndrome. The concept of "vital exhaustion" (37, 38), in which exhaustion is a risk factor for later CVD has not been studied among shift workers either. Not only can stress lead to sleep problems, lack of sleep has also been described as a stressor (39) and through this action can be regarded as a potential risk factor. The stress of sleep deprivation is discussed later in this article. In conclusion, exhaustion, sleep apnea, and exposure to circadian mismatch may be risk factors, but no literature links shift work with them.

Disturbed sociotemporal patterns, social support and stress

Another well-known consequence of shift work is problems in family life, as the workhours interfere with social activities, reduce the time available for both family and recreation, and potentially lead to social isolation and subsequent stress.

Social support has emerged as a risk factor for CVD (40), and, since one of the main causes of stress among shift workers is problems with the relationship between family life and worklife, social support could be of importance in the interaction between shift work and CVD. The risk is individually tied to the actual family pattern and to the dynamics of familial interactions and, therefore, is difficult to measure. No studies have attempted to examine the social support of shift working families in relation to the occurrence of CVD among shift workers.

Stress is probably one of the key elements in the relationship between shift work and disease. The definition of stress varies, but in general it can be anticipated as "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being [p 19]" (41). This definition implies that people respond differently to similar stressors. In occupational settings stress has been defined according to demand and decision latitude, person-environment misfit, and effort-reward imbalance. Stress defined according to Lazarus has been related to changes in cholesterol (42), but not to CVD end points. The strain model and the effort-reward imbalance model are both associated with myocardial infarction (43, 44), but it is unclear whether these

models adequately measure the specific kind of stress that is associated with shift work [in relation to conflicts between roles in family and worklife and the physiological desynchronization of circadian rhythms possibly leading to sleep disturbances (45—51)].

The possible mechanisms linking stressful experiences to psychophysiological changes have been extensively studied (52), but only 1 investigation (53) has examined the relationship between shift work, stress, and cardiovascular risk factors. This study measured glycated hemoglobin as a marker of catabolic drive and found higher values for shift workers than for day workers. The shift workers were, however, also subject to other stressors in the work environment (eg, noise and overtime).

Both a possible effect of social support and a possible effect of stress on shift workers' risk of CVD have received remarkably little attention in the literature.

Behavioral changes

Both as a consequence of stress, eventually acting through attempts to cope with the stressors of shift work, and as a direct consequence of poor work conditions in general (closed canteens at night), the life-style of shift workers and day-working colleagues may differ. Studies on the behavior of shift and day workers are presented in table 2.

Being one of the most important risk factors for CVD, tobacco use may constitute an important part of the path between shift work and CVD, providing that shift workers smoke more than their day-working counterparts. Six (54—59) of 13 cross-sectional studies found that shift workers smoke significantly more than day-working referents (table 2). One study (60) found that shift workers smoked less than day workers, and the rest did not find any differences (48, 61—64). In the 2 cohort studies for which characteristics can be evaluated (8, 22), shift workers smoked significantly more than day workers at the beginning of the study. In the relative short prospective studies (up to a year of follow-up) of new shift workers or following changes in shift schedules, the shift workers did not tend to start smoking or change smoking habits (65, 66). This finding suggests that the smoking habits of shift workers change slowly. In the 7 "positive" studies the quantitative differences were 10—40%. In none of the studies that attempted to control for tobacco consumption did smoking habits in full explain the increased risk.

Use of alcohol in a moderate amount has been found to be protective from CVD (67). In 10 studies alcohol consumption was addressed. Six cross-sectional (56, 58, 60—62, 64) and 1 prospective study (68) did not find any difference between day and shift workers, while 1 study found a smaller (63) and 2 studies (22, 48) a larger alcohol consumption among shift workers. One of the studies measured gamma glutamyl transferase, aspartate

Table 2. Studies on life-style-related risk factors among shift workers. If not otherwise stated, the first value is shift worker, the other day worker. Statistically significant results are marked in italics. If results are stated without quoting the actual numbers, "+" or "0" is used for statistically significant and nonsignificant differences.

Reference ^a	Persons	Tobacco smokers (%)	Alcohol users (%)	Diet	Exercise	Body mass index kg/m ²
<i>Cross-sectional and cohort study base line</i>						
Thelle, 1976 (54) (x)	1291 shift workers, 5224 day workers	64.9/54.8	.	.	.	Weight: 76.6/74.7
Michel-Briand, 1986 (61) (x)	99 shift workers, 93 day workers	51/53	0	.	.	.
Gordon, 1986 (48) (x)	1661 shift workers, ? day work + fixed night workers	0	+	.	.	.
Knutsson, 1986 (8) (xxx)	394 shift workers, 110 day workers	74/50	.	.	.	.
De Backer, 1987 (62) (xx)	243 shift workers, 401 day workers	48/40	20.8/20.7	0	0	24.9/24.7
Knutsson, 1988 (55) (xxx)	361 shift workers, 240 day workers	54/39	.	.	.	25.8/25.9
Knutsson, 1989 (56) (xxx)	329 shift workers, 233 day workers	43/33	0	.	.	.
Cesana, 1990 (57) (x)	150 shift workers, 150 day workers	+	.	.	.	0
Burse, 1990 (74) (x)	57 shift workers, 57 day workers	Matched	.	.	.	0
Costa, 1990 (60) (x)	158 shift workers, 44 day workers	22/39	49.3/48.6	.	74.1/81.8	26.1/25.6
Romon, 1992 (63) (xxx)	73 shift workers, 73 day workers	Cigarettes/day 15.4/13.9	Grams/day: 9.3/15.6	0 (energy, carbohydrates, fat)	Matched	24.6/24.7
Lasfargues, 1996 (58) (xx)	1400 shift workers, 1400 day workers	Men: 46.2/38.4, women: 41.9/32.3	Grams/day: men: 23/25, women: 2/5	More water and milk, missing meals	>1 hour/day: 58.9/55.9, women: 50.7/26.7	Men: 25.3/24.8, women: 23.7/22.7
Nakamura et al, 1997 (64) (xxx)	33 shift workers, 239 day workers	76.9/71.6	Everyday: 54/40	.	Never: 69.2/50.2	23.4/23.0
Knutsson, 1998 (59) (xx)	906 shift workers, 4514 day workers	Men: 24/22, women: 31/27	.	.	.	.
Bøggild, 1998 (22) (xx)	1123 shift workers, 4084 day workers	76.1/71.0	Grams/day among users: 17.7/16.8	.	Fitness value (VO ₂): 33.4/32.7	Weight (kg): 78.0/76.9
<i>Prospective studies</i>						
Theorell, 1976 (68) (xxx)	33 shift workers, own referents	0	0	0	0	.
Orth-Gomér, 1983 (65) (xxx)	46 shift workers, clockwise and counterclockwise, own referents	4.7 (cigarettes/shift)/ 4.4	.	.	.	0
Knutsson, 1990 (66) (xx)	12 shift workers, 13 day workers	0	.	+ (dietary fibers)	.	.
Lennernäs, 1994 (31) (xxx)	22 shift workers, own referents	.	.	+ (distribution)	.	.

^a Overall quality of study, based on Kristensen (2) is given (range from x to xxxxx).

aminotransferase, and alanine aminotransferase as markers of alcohol consumption without finding any difference (56) between the day and shift workers.

Especially the ratio between saturated and polyunsaturated fat in the diet has been established as a risk factor for CVD, but also the amount of energy coming from fat is an independent risk (69). The diet of shift workers has been examined in 13 studies, recently evaluated by Lennernäs in her dissertation (70). The studies on diet have demonstrated only few differences between shift and day workers with regard to nutritional intake, but changes in meal frequency and the timing of meal intake among shift

workers were reported in several studies. Six studies correlated nutritional data with biomarkers for CVD. In 2 cross-sectional studies there were no differences between shift and day workers with respect to energy, carbohydrates, fat, or protein (62, 63), while 1 study found that shift workers drink more milk and water, and they miss meals (58), all without concurrent differences in biomarkers. In the prospective studies a more frequent use of snacks with a high amount of single carbohydrates at night (66) and a change in distribution was seen (31, 71). One prospective study did not find dietary differences (68) between day and night workers. The change in meal

distribution was associated with changes in cholesterol (31), which was seen as a result of circadian desynchronization of uptake and metabolism.

Regular exercise is protective from CVD (72). In 3 studies (58, 60, 62) no differences in exercise habits were found, while 1 study found (58) that a higher proportion of female shift workers used more than 1 hour a day to exercise. One prospective study found no differences in exercise patterns between working a day shift and working a night shift (68), one found a higher proportion of persons doing exercise among day workers (64), while a cohort study found the shift workers to have higher fitness values at the beginning of the study (22).

Differences in nutrition and exercise habits eventually lead to differences in weight, and moderate overweight has been found to be a risk factor for CVD (73). In 8 studies of shift workers (55, 57, 60, 62–65, 74), in which the question has been addressed, no difference in either weight or body mass index was reported. Two studies found that shift workers were heavier than day workers (22, 58). An interesting but unsettled issue has recently been raised by Nakamura et al (64), who found that, although the body mass index was the same for day and shift workers, shift workers had more centrally disposed adipose tissue, which has been found to be a risk factor of CVD.

Biological mechanisms (biomarkers)

The evolution of CVD is slow and probably consists of 2 partly separated processes, a slowly atherosclerotic process and later thrombosis (29, 75). It is assumed that manifest illness is preceded by changes in the concentration of markers of these processes, and they are thus regarded as biomarkers of subclinical disease (76). The best examined markers are cholesterol and other lipids [triglyceride and apolipoproteins, fraction A and B (Apo A, Apo B)] (29, 77, 78), reflecting atherosclerosis. Other markers mirror the coagulation and fibrinolytic processes, among these thrombocytes, fibrinogen (79), factor VIIc (80, 81), the fibrinolysis products tissue plasminogen activator (t-PA), tissue plasminogen activator inhibitor (t-PAI), and complement (75), all of which have been found to be independent risk factors. Glycated hemoglobin (HbA1c), which reflects glucose metabolism and thus acts as a biomarker of stress (82, 83), has also been shown to be an established risk factor for CVD (84). High blood pressure and electrocardiographic signs of hypertrophy are also established risk factors, which have been regarded as biomarkers in this review.

The literature search revealed 27 studies on biomarkers of CVD in shift workers. Most of the studies are presented in table 3.

In 10 of 16 investigations cholesterol levels did not differ between day and shift workers (table 3) (55, 57,

60, 62, 63, 65, 74, 85–87), while 5 studies found higher values for shift workers or higher values related to different organizations of shift work (31, 54, 64, 66, 68). One study found lower values among male shift workers, but no differences among women (58). In 3 (31, 66, 68) of 6 (31, 65, 66, 68, 86, 87) prospective studies, significant changes in cholesterol were found. The magnitude of change in studies with significant differences was between 3% and 20%. Differences in the high-density lipoprotein (HDL) and low-density lipoprotein (LDL) fractions of cholesterol were assessed in 3 cross-sectional studies (60, 62, 63), and no statistically significant difference was found. In 1 longitudinal study (31) a correlation between diet and the LDL:HDL ratio was found, and in another there was a decrease in the LDL:HDL ratio at the change to fewer night shifts in a row (87), while 1 study did not find changes (86).

Apolipoprotein has been measured at the change from day to shift work. A statistically significant increase in ApoB and, accordingly, an increase in the ApoB:ApoA1 ratio (66) was found. In a cross-sectional study (88) no difference was found between shift and day workers.

Triglyceride has been measured in 12 studies (54, 55, 57, 58, 60, 62–66, 86, 87), among which 4 found statistically higher values among shift workers (55, 58, 63, 65). Orth-Gomér (65) found higher values for counter clockwise than clockwise rotation (from day to evening to night shift rather than from day to night to evening shift).

Plasminogen activator and tissue plasminogen activator inhibitor (t-PA and t-PAI) were measured (89) as indicators for the fibrinolytic system and were found to include both a phase shift and a reduction in amplitude in shift workers. This finding suggests that the dissolution of thrombi could be slower due to the lower activity. One study (85) found higher fibrinogen levels among shift workers than among day workers.

In 9 (22, 54, 55, 57, 58, 63, 64, 74, 85) of 19 studies on blood pressure or hypertension, there were no differences between day and shift workers. Two studies found more hypertensive subjects among the day workers (61, 90), one found a lower (91) and one (60) found a higher diastolic pressure among shift workers, and one a higher (65) and one a lower systolic pressure (92). Three studies have measured 24-hour blood pressure (93–95), of which one found (94) that the high plateau of both systolic and diastolic pressures in the nightshift workers were longer, although no difference in the mean pressure was found. The differences between the shift and day workers were small [maximum 3 mm Hg (0.40 kPa) higher diastolic blood pressure]. Such differences have been associated with a 10% higher risk of CVD (77), and this finding suggests that changes in blood pressure were not solely responsible for the relation. A German review (96) concluded that there is no relationship between shift work and higher risk of hypertension.

Table 3. Studies on biomarkers for cardiovascular diseases among shift workers. If not otherwise stated, the first value is shift worker, the other day worker. Statistically significant results are marked in italics. If the results are stated without the actual numbers being quoted, "+" and "-" have been used as statistically significant positive and negative associations, and "0" as nonsignificant changes. (LDL = low-density lipoprotein, HDL = high-density lipoprotein, S = mean systolic pressure, D = mean diastolic pressure, HbA1c = glycated hemoglobin, * = circadian rhythms varied between shift and day workers, 24 h = 24-hour ambulatory pressure, t-PAI = tissue plasminogen activator inhibitor)

Reference ^a	Persons	Cholesterol (mmol/l)	LDL/HDL-cholesterol (mmol/l)	Triglycerides (mmol/l)	Apo-protein (mmol/l)	Blood pressure	Other biomarkers
<i>Cross sectional and baseline cohort studies</i>							
Thelle, 1976 (54) (x)	1291 shift workers, 5224 day workers	6.79/6.58	.	1.48/1.41	.	S: 127.2/126.3, D: 79.1/77.5	.
Fouriaud, 1984 (92) (x)	94 shift workers, 2640 day workers (women)	.	.	.	.	S: 125.3/130.1	.
Cesana, 1985 (53) (x)	100 shift workers, 200 day workers	.	.	.	.	.	HbA1c: 8.04/7.40
De Backer, 1987 (62) (xx)	243 shift workers, 401 day workers	5.21/5.28	Ratio: 32/32	4.7/4.7	.	.	.
Knutsson, 1988 (55) (xxx)	361 shift workers, 240 day workers	5.96/5.95	.	1.61/1.43	.	S: 139.7/139.7, D: 83.0/83.3	.
Lang, 1988 (90) (xx)	396 shift workers, 900 day workers	.	.	.	.	S: 129.7/125.3, D: 75.6/74.9	.
Cesana, 1990 (57) (x)	150 shift workers, 150 day workers	0	.	0	.	.	.
Costa, 1990 (60) (x)	158 shift workers, 44 day workers	5.50/5.80	HDL: 52.6/53.9	149.4/144.3	.	S: 135.0/137.5, D: 89.1/86.9	.
Burse, 1990 (74) (x)	57 shift workers, 57 day workers	5.68/6.19	.	.	.	S: 125.1/124.0, D: 77.6/78.7	.
Romon, 1992 (63, 88) (xxx)	73 shift workers, 73 day workers	5.50/5.45	HDL: 1.21/1.26	1.26/1.03	ApoA1/B-ratio: XX 1.21/1.32	S: 135/134, D: 85.1/86.1	.
Lasfargues, 1996 (58) (xx)	1200 shift workers, 1200 day workers	Men: 5.81/5.91, women: 5.24/5.32	.	Men: 1.65/1.33, women: 0.9/0.8	.	Men: S: 132/133, D: 83/83; women: S: 120/120, D: 78/78	Leucocytes: men: 7.8/6.8, women: 7.6/6.6
Netterström, 1996 (85) (x)	68 shift workers, 1079 day workers	0	.	.	.	0	Fibrinogen: 2.88/2.66
Nakamura, 1997 (64) (xxx)	33 shift workers, 239 day workers	5.70/4.98	.	1.70/1.58	.	S: 127.5/129.4, D: 76.7/75.5	.
Bøggild, 1998 (22) (xx)	1123 shift workers, 4084 day workers	.	.	.	.	S: 136/135, D: 83/83	.
<i>Prospective and cohort studies</i>							
Theorell, 1976 (68) (xxx)	33 shift workers, own referents day/night shift; relative changes	0.96/1.02	.	.	.	.	Total lipids: 0.96/1.03
Peacock, 1983 (91) (xxx)	75 shift workers, own referents	.	.	.	.	S:0, D:-	.
Orth-Gomér, 1983 (65) (xxx) (from figure)	46 shift workers, clockwise/ counter-clockwise rotation	-4/-6 ^b	.	-4/15 ^b	.	S: 111.6/115.6, D: 75.2/75.8	.
Fredén, 1984 (86) (x)	18 shift workers	0	HDL: 0	0	.	.	.
Sundberg, 1987 (93) (xxx)	7 shift workers	.	.	.	.	24 h: 0 (*)	.
Chau, 1989 (94) (xxx)	15 shift workers	.	.	.	.	24 h: + (*)	.
Baumgart, 1989 (95) (xx)	17 shift workers	.	.	.	.	24 h: 0	.
Peternel, 1990 (89) (xxx)	10 shift workers, 10 day workers	.	.	.	.	.	t-PAI: + (*)
Knutsson, 1990 (66) (xx)	12 shift workers, 13 day workers	5.0/4.0	.	1.0/1.0	ApoB: 0.84/1.03	S: 132/124, D: 71/68	.
Lennernäs, 1994 (31) (xxx)	22 shift workers	+	Ratio: +	.	.	.	.
Kecklund, 1994 (87) (xxx)	60 shift workers, 15 day workers (before-after)	5.4—5.4/ 5.4—5.5	Ratio: 3.1— 2.7/ 3.2—3.4	1.2—1.2/ 1.3—1.4	.	S: 132/127 D: 84/81	.

^a Overall quality of study, based on Kristensen (2); is given (range from x to xxxxx).

^b Percentage of change.

Bursey (74) obtained electrocardiograms from day and shift workers and found no differences in the number of normal recordings (68.4% versus 61.4%). One study (34) found a higher number of ventricular extrasystoles in nightshift than in dayshift when the subjects were measured with 24-hour Holter monitoring.

In 5 studies biomarkers for CVD have been evaluated in 24-hour measurements. In one study 24-hour blood pressure was found to shift in parallel but without a change in the mean pressure (93), while another study (94) found a longer plateau with a high diastolic and systolic pressure. A 3rd study on blood pressure found no differences, apart from a phase shift in parallel with the workhours (95), while a 4th (34) found more ventricular extrasystolic beats in shift workers than in day workers. In the 5th study fibrinolytic activity had a lower level in the night shift workers and presumably led to a higher risk of thrombosis (89).

Most studies have thus concentrated on markers of atherosclerosis. Although no firm conclusion can be drawn, both cholesterol and triglycerides seem to be raised, primarily in the methodologically better studies and especially in the few prospective studies. Changes were observed in the predicted direction of higher biomarkers for shift workers in all but 1 study (58).

General methodological problems

The studies have used very different methodological approaches. Despite the heterogeneity of study design, some problems relate to all studies. One such problem is related to "exposure". There is no commonly accepted definition of shift work, and it encompasses at least 3 different modalities, that of the type of shift work (rotating or fixed, including or excluding night work, continuous or discontinuous, ie, including or excluding week-ends), the schedule [number of night shifts in a row, rotating clock- or counterclockwise and other ergonomic criteria for shiftwork scheduling (97)], and the amount of night and evening work (number of night shifts a month). Only a few of the studies have described the work schedule in detail or have included information on the "dose" of exposure, for example, in terms of years of shift work. In the American tradition, the problem of shift work relates to the rotation of work, while Europeans are concerned also with night work in itself (98, 99). As a consequence, 2 American studies and 1 European study (17, 48, 92) included fixed night workers in the reference groups.

The "lifetime" exposure required to be labeled as a shift worker ranges from prevalent self-reported shift work to more than 10 years as a shift worker in the same factory (21). In a subsample of studies, exposure was attached to certain occupations on an aggregated basis, often based on interviews of a smaller sample (14, 16, 25, 100). This approach leads to a misclassification of expo-

sure, as many of the workers in the exposed occupations were in fact not shift workers and would thus be suspected to give lower risk estimates. This expectation is however not fulfilled. These studies tended to show higher risk estimates than studies with an individual exposure classification.

In some studies shift work takes place in an industrial setting, often comprising 7–8 nights a month, while others have had the cut off point at 3 shifts (being afternoon or nights) a month (17). Therefore the exposures are generally not comparable, and the exposure in some studies is very weak. Day workers may furthermore be former shift workers; in such cases the exposure contrast between day and shift workers becomes very small (19).

Another issue is the definition of outcome. The epidemiologic studies have used different definitions of CVD and the narrower term ischemic heart disease, and in 1 study also hypotension and varicosis were included (26). Some have dealt only with mortality figures on myocardial infarction, whereas others have also included angina pectoris and myocardial infarction morbidity. Some of the studies have exploited registers of hospital discharges, while others have blindly examined records in order to establish the diagnosis. Strict definitions are only very seldom reported (101), and sudden death is not always included in CVD.

The overall impression is, however, that newer studies have stricter diagnostic criteria. Most studies have combined information on both morbidity and mortality. Two studies (19, 21) used only mortality figures. Both of them found no connection between shift work and CVD. As 70% of myocardial infarction patients survive and as both etiology and personality between survivors and nonsurvivors may differ, it would be advisable to distinguish between these factors in future studies.

Many biochemical factors are subjected to circadian rhythm, among these also several of the biomarkers discussed. In a study of day-oriented healthy subjects, the circadian rhythm attributed to 39% of the daily variation in triglycerides, the corresponding value being 30–34% for the total, LDL and HDL cholesterol concentrations, and 11% for apolipoprotein (102). Thus the timing of blood sampling is important to comparisons of measurements between day and shift workers or between shift workers in different phases of their schedules. If blood samples are drawn immediately after a night shift, the values may be elevated, not due to the effect of shift work, but, instead, because the measurement was done in different phases of the circadian rhythm of the biomarker. Many of the studies reporting on biomarkers do not explicitly state the duration between night work and blood sampling.

We have tried to evaluate the importance of some of these problems for the outcome of the epidemiologic studies. This evaluation involved ranking the studies ac-

cording to the amount of shift work needed to be included in the shift work group and examining whether this procedure led to a pattern in the outcome. Second, we ranked the studies by diagnostic entity. Third, we ranked by the quality judgment attached to the studies. Neither of these rankings showed any particular pattern in risk estimation, except that the methodologically best studies (labeled xxx and xxxx in table 1) in general show risk estimates of around 1.4 and narrow confidence intervals.

The 4th problem relates to the selection of comparison groups. The appropriateness of this group is of paramount importance, and the ideal group should resemble the shift workers in all ways (at least regarding risk factors for CVD) than the worktime schedule. In almost all of the studies, the reference groups are not truly comparable in the sense that they are "what the shift workers would be, had they not worked at night".

In many studies it has been problematic to find relevant reference groups, as shift work is often used for only certain functions in a company. Shift work is clearly related to socioeconomic status, as it is more prevalent among unskilled workers and lower civil servants (7, 103). CVD is known to be related to socioeconomic status (104), and therefore socioeconomic status is a potential confounder, especially in studies with the general population as reference. Day-working reference groups may be skilled workers in contrast to unskilled shift workers, and thereby the comparison is done between different socioeconomic groups, with different cultural backgrounds and with differences in life-style. As CVD is known to be more widespread among lower socioeconomic groups, confounding would lead to higher risk estimates. A few epidemiologic studies have controlled for social class, and, in 2 of them, the effect of controlling can be examined. Tenkanen et al (18) analyzed blue-collar day and shift workers alone and found that the relative risks fell. Likewise Bøggild et al (22) controlled for social class by restricting analyses to 1 social class and found that the risk estimates fell below unity. In the study by McNamee (19) initial job status was controlled for; Kawachi (17) studied only nurses and also controlled for education of spouse; and in the study by Knutsson et al (15) control was made for educational level. In most of the studies, including studies on risk factors, social class differences have not been controlled and may have confounded the results. In contrast, shift workers often earn more or hold a second job.

People choosing to work in shifts are self-selected and are known to differ from day workers in terms of sleeping habits and rigidity of sleep. One study (62) examined whether shift workers differed from day workers in personality traits (type A) that have been linked to CVD (105). This was not found to be the case.

Age is the major risk factor for CVD, and in general shift workers tend to be younger than day workers at the

same factories, as day work is, in many instances, a "reward" for some years of shift work. Most epidemiologic studies have controlled for age, but 3 older studies did not (61, 106, 107), and this omission may explain the "negative" finding of all 3 studies.

Work conditions may differ between shift and day workers in terms of risk factors for CVD (eg, cardiotoxic chemicals, environmental smoke, monotonous or sedentary surveillance work), and may thus act as a confounder for CVD. Only few of the studies report details on work conditions. The direction of this confounding is not predictable, but would probably tend to overestimate the risk. One study found no differences in exposure to environmental smoke between day and shift workers (59).

Day and night work may, for instance, differ in terms of the amount of job strain. Indirectly the importance can be evaluated from the Helsinki Heart Study (18), which provided questionnaire responses about job decision latitude and psychological demands. Comparing these figures for day and 3-shift workers showed that shift workers in "industry work in plant or machine operation" have the same demands but much lower decision latitude than day workers. In another study (15) shift workers experienced more strain than day workers, but control for the differences did not change the risk estimates. In a study of nearly 1000 Swedish subjects engaged in driving, industrial work, police work, or cooking, day-working women experienced higher job strain than shift-working women, while no differences were present for the men (108).

One of the most important methodological problems in shiftwork research is the selection process both into and out of shift work (11). Primary selection into shift work is both due to the applicant and to the company. People applying for shift work may differ from people choosing not to apply, on the basis of the applicants' estimate of their own ability to cope with worktime on the job. Companies may select applicants on the basis of preemployment testing, which may also lead to differences between shift and day workers. This primary selection is uncontrollable, but would probably lead to an underestimation of the true risk.

Secondary selection takes place when the shift worker moves out of shift work. In some instances the move is forced by organizational changes, but it can also be due to medical or social reasons, depending on, for example, feelings of stress, problems with sleep, and the like. These selection processes are probably also of major importance in relation to CVD, as can be seen from ex-shift workers' risk, which is often higher than that of current shift workers (21, 109) — Taylor & Pocock's (21) finding, in their cohort study, was a standardized mortality ratio of 160 (95% CI 121.5—210.4) (reanalyzed by us). In 1 study sick leaves for CVD among employees

transferred to day work for medical reasons were more numerous than among shift workers, while transfers due to organizational changes led to the same incidence of sick leaves as that of the day workers (110); this finding suggests that people being at risk of CVD are somehow warned or that causal mechanisms interact with risk factors for other diseases or well-being and lead to selection.

As most of the unaggregated cohort studies (17, 18, 21, 22) include subjects in their 40s, half a worklife may have, in many instances, passed before inclusion, and the selection processes may have played their role. Differences in possibilities for changing work may therefore in part account for the differences found.

The exposure being relatively hard, information bias is probably not very important. In his thesis (30) Knutsson found that a double check between self-stated shift work and personnel records in general showed good agreement between the two. As stated, the exposure in many studies has been measured at one point in time, and, if years of shift work is to be used as an exposure variable, the issue needs to be dealt with.

Many of the reviewed studies have controlled for factors that, in reality, are not confounders, but are instead mediating factors and links in the causal chain between shift work and CVD. This possibility may have led to real differences being hidden.

Discussion

Seventeen studies dealing with the risk of CVD in people working outside daily workhours were identified. Four large studies did not support a relationship, and, although methodological problems are also present in these studies, the overall quality is not poorer than the majority. On balance, however, the most convincing study (8) demonstrating a dose-response relationship 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. The apparent heterogeneity of the results may be due to different settings, the ability to find other jobs being a possible explanation. There is, therefore, still a need for epidemiologic studies examining the relationship between shift work and CVD, but the research would have to be more carefully designed.

The causes of the relationship between shift work and CVD have only partly been dealt with. Of 3 suggested major pathways for CVD in shift workers, only 1 pathway has been elucidated in any detail. The literature has focused on life-style changes, and, of these, differences in smoking and diet seem to be important, while alcohol and exercise habits are not. Life-style does not seem to explain more than part of the relationship, however, and one reason for the conflicting results on alcohol, diet, and

exercise may be due to these life-style factors also being culture-dependent, a factor that, therefore, leads to shift workers in different countries experiencing different life-style changes.

The other pathways, changes in circadian rhythm, and social disruption have received very little attention. The changing circadian rhythm has been dealt with sparsely. It could explain the behavior of biomarkers (higher cholesterol and triglyceride levels), but one cannot exclude a separate importance of, for example, a changed pattern of fibrinogenic activity. The question of social support, stress, and sleepiness has not been studied at all, even though they are both common effects of shift work and also established risk factors for CVD. Future studies would have to look into these areas.

For biomarkers, the focus has been on blood pressure as a marker of sympathetic and parasympathic activity. Twenty-four-hour blood pressure may, on the average, be slightly higher for night workers, but not to a degree that reaches hypertension, and not enough to explain a relative risk of 1.4.

Cholesterol and triglycerides have been studied on several occasions. In the methodologically most convincing studies, shift workers have had slightly elevated values.

Methodological problems are related to the majority of studies, major concerns relating to noncomparable reference groups in terms of social class and different job functions, vague and irrelevant exposure variables, and, especially in early studies, ill-defined outcome variables.

One crucial methodological challenge would be to find suitable reference groups. Much effort should be given to the selection of these groups, as the comparability should be maintained at the highest level. If day workers are used, it would seem to be necessary to control at least for differences in social class (educational level, income, prestige), personality factors (hostility), and the work environment. Another solution would be to include factories in which the use of shift work had been abandoned and follow these former shift workers as referents, as they would probably resemble the shift workers more closely in relation to personality and social class. Selection should be accounted for.

Ideally, studies should incorporate knowledge on the risk factors for CVD and should not control for information on factors that are essential to the mediation of the relationship. The primary risk factors have often been treated as confounders, but they can also, as, for example, tobacco consumption, be higher due to shift work and should be treated as mediating relations and as part of a causal web.

Exposure should be expanded to include fixed night shifts. Three studies have analyzed fixed night work (14, 15, 20), two suggesting that it confers the same risk as rotating shifts. Different shift schedules should be dis-

tinguished to identify which type of shift schedule confers the smallest risk. In addition the amount of night work in a shift and the inclusion or exclusion of weekends should be looked into. Of special interest would be to study the impact of ergonomically designed shift schedules that aim at lowering the strain of shift work (97), to investigate whether this change would lower biomarkers for CVD and lead to lower risk of CVD in the long run. The results of intervention studies on risk factors for CVD (65, 87) suggest that scheduling can be done in a way that leads to lower risk factors. This is crucial knowledge for primary prevention purposes, but it needs to be expanded.

The traditional 3-shift schedule is increasingly being replaced by flexible worktime arrangements, in which employees are expected to work in more irregular shift systems or with longer workhours. It would be valuable to expand the research to cover these areas, as the irregularity could put further strain on shift workers' social life, depending on the degree of control given to the employee.

Future clinical epidemiologic studies on risk factors in shift workers should include markers of both atherosclerosis and hemostasis, and attention should be paid to the circadian rhythm of the biomarkers. Blood sampling should be made either several times a day, to establish its circadian rhythm, or after several days of day orientation, as the values may reflect different time slots instead of real differences. Intervention studies should be attempted that change the shift schedule and follow the employee during this process.

Two important questions relating to prevention have not been answered: "Is the effect of shift work acute or chronic?" and "Does the effect hit by chance or are people susceptible at the individual level on the basis of biological differences, social life circumstances, or patterns of other risk factors?" In relation to the first, the patterns of myocardial infarction, with a mismatch of oxygen supply and need, could indicate that night work leads to acute effects. In this case it would not be appropriate to study long-term clinical effects, since focus should rather be on the effects of changes in night work on the cardiovascular system in laboratory settings, in studies on people with and those without overt cardiovascular disease. As for the second question, studies on the interaction of risk factors suggest that the answer could be affirmative. Both in the Helsinki Heart Study (111) and in the Swedish SHEEP study powerful interactions between shift work, body mass index, physical activity, and smoking have been found. The implication could be that certain people undergo a large additional risk, while others could be unaffected. This issue of individual susceptibility also needs further enlightening.

The goal of studying shift work and cardiovascular disease should eventually be the ability to prevent dis-

ease. No single mechanism seems to be working. Shift workers should probably be advised to maintain healthy life-style habits, especially regarding smoking, and should eat regularly, also on night shifts. Such recommendations concern, however, only part of the issue, as the two other causal mechanisms are not covered (112). A few studies show that the organization of shift work is important; that is, whether the shifts rotate clockwise or counterclockwise (65) and have few or many nights in a row (87) have an explanatory value in themselves on biomarkers of CVD, irrespective of smoking and diet. The impact of this knowledge is potentially of great significance because changes in work organization come closest to helping eliminate exposure.

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