

Shift work and heart disease

Epidemiological and risk factor aspects

Ph.D. thesis

Henrik Bøggild

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Praise be doubt! I advise you to greet
Cheerfully and with respect the man
Who tests your word like a bad penny.
I'd like you to be wise and not to give
Your word with too much assurance.

Bertolt Brecht

“In praise of doubt”
Brecht Poems 1913-1956
Methuen Publishers

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The original idea for some of the studies, that this thesis is based upon originates more than 10 years ago, before I even knew that shift workers presumably had a higher risk of heart disease. Hans Jeppe Jeppesen, psychologist at the Department of Occupational Medicine in Aalborg, upon reading a study by Knutsson and coworkers, drafted an idea for an intervention study. Shortly after I started working at the Department in 1991, he introduced me to the field of shift work and - well - we have been working together since. Thank you, Jeppe, for many hours of discussions and cooperation. I guess we have learned a lot from each other and maybe brought medicine and psychology a little closer together.

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The thesis is based upon the following publications, referred to in the text by their roman numerals:

- I: Henrik Bøggild and Anders Knutsson. Shift work, risk factors and cardiovascular disease. Scand J Work Environ Health; 1999; 25: 85-99
- II: Henrik Bøggild, Poul Suadicani, Hans Ole Hein and Finn Gyntelberg. Shift work, social class, and ischaemic heart disease in middle aged and elderly men: a 22 year follow up in the Copenhagen Male Study. Occup Environ Med 1999; 56: 640-5
- III: Henrik Bøggild, Hermann Burr, Finn Tüchsen and Hans Jeppe Jeppesen. Work environment among Danish shift and day workers (manuscript)
- IV: Henrik Bøggild and Hans Jeppe Jeppesen. Intervention in shift schedule and change in biomarkers of heart disease and stress at hospital wards (manuscript)
- V: Henrik Bøggild and Hans Jeppe Jeppesen. Shift schedule characteristics and biomarkers of stress and heart disease (manuscript)

Abbreviations:

AP	Angina pectoris	RRPA	Rota Risk Profile Analysis
Apo-A	Apolipoprotein A	RE	Regularity
Apo-B	Apolipoprotein B	PE	Periodicity
BMI	Body Mass Index	LS	Load/shift
CI	Confidence interval	LW	Load/week
CMS	Copenhagen Male Study	ON	Opportunity for rest at night
CVD	Cardiovascular disease	PE	Predictability
HbA _{1c}	Glycated hemoglobin	OH	Opportunity for household activities
HDL	High density lipoproteins	OE	Opportunity for evening activities
IHD	Ischaemic heart disease	OW	Opportunity for weekend recreation
LDL	Low density lipoproteins		
MI	Myocardial infarction		
OR	Odds ratio		
NARFE	Not an abbreviation; A giant from Nordic mythology, the father of day and grandfather of night		
NWECS	National work environment cohort study		
t-PAI	tissue-Plasminogen activator inhibitor		
RR	Relative rate ratio		
TC	total cholesterol		
TG	triglycerides		
WHR	Waist Hip Ratio		

Introduction

Shift work was not a consequence of the industrial revolution - The monks of the monastery, guards at the castle, and seafarers have been at work at odd hours since biblical times. And the hazards (albeit not heart disease) of night work was recognized by the father of occupational medicine, Bernardino Ramazzini (1633-1714), who wrote in "De Morbis Artificum" (1713) that bakers "work at night, and when other men have finished the day's task and are asleep recruiting their energies, they must work all night and sleep all day, like bats". Also learned men working by the burning oil lamps have "the spirits (diverted) to other organs (causing) their stomachs to abound in the acid of undigested food..." (quoted from Harrington¹ (p. 3)). Whether gastrointestinal problems are suggested caused by "spirits" or metabolic desynchronization the shift worker have at all times recognised that working hours in the night influenced their health.

The knowledge of an apparent risk of heart disease is of newer date. The first studies dealing with shift work and heart disease was conducted in Norway by plant physicians, Thiis-Evensen at Norsk Hydro, Porsgrunn² and Aanonsen at electrochemical plants in Odda³. Heart disease was included as part of studying morbidity in broader sense. Both studies have been regarded as essentially negative but when reanalysing the study by Thiis-Evensen, a higher risk is detected (I). The first cohort study⁴ was also interpreted as not showing any differences. It did, however, show that workers having left shift work had a higher risk of heart disease. With the fairly inconclusive literature Harrington concluded in his classical review of shift work and health that "no excess cardiovascular (...) morbidity or mortality has been demonstrated" (p. 19)¹

A second wave of studies on shift work and heart disease was published from the beginning of the 1980'ies and with three Swedish studies⁵⁻⁷ in the process of publication the first review to suggest an association between shift work and heart disease was published in 1984⁸. Especially the historical cohort study of 504 papermill workers by Knutsson et al⁷ has been influential, as it was well conducted and showed an increasing risk with increasing number of years on shift work.

Since then, the number of epidemiological studies has slowly increased and recent reviews both of shift work and health in general⁹⁻¹², on work environment and heart disease¹³⁻¹⁵, and on shift work and heart disease in particular^{16,17} all conclude that shift work and heart disease is associated.

At the same time, studies on the possible causes of this relationship have been published, suggesting that the risk could be conferred through traditional factors like smoking, blood pressure and diet (I).

Another type of study related shift scheduling and the introduction of ergonomic criterias for scheduling to health and well-being, and a single study had shown that rotation with the clock led to lower triglycerides and glucose than counter clockwise rotation¹⁸. This prompted the idea that the risk of heart disease among shift workers could be reduced through the design of shift schedules.

When we started the research related to this thesis in 1993, I was rather convinced by the reviews. The work has broadened through the period and this thesis examines whether the relationship between shift work and heart disease is causal, a prerequisite for rational prevention.

Background

Shift work

There is no universally accepted definition of shift work. It encompasses situations where working hours are at least partly situated outside normal day work. Day work, however, also lacks a definition, often just being stated by two clock hours for instance between 6 am and 6 pm but differing from country to country.

Shift work covers a temporal organisation of work that includes part or all evening and night hours. In some definitions, among others the one used by ILO¹⁹, shift work is further delimited to situations where crews or teams alternate to ensure a continuous operation. In this definition, shift work would not cover for instance waiters, who would instead be labeled as having permanent displaced evening work.

In this thesis shift work is used in the broader sense and defined as "work outside normal day working hours". Others would not regard this as shift work, but it was chosen as the effect of working hours is probably not related to whether the shift workers is alternating with others or not.

Shift work may be organised in very different ways, several hundreds schedules being described in the literature²⁰. In the perspective of the shift worker the organisation of the shifts in a shift schedule is viewed in terms of having either one or more types of shifts. In the first instance where working hours for instance are always 3 pm to 11 pm or from 11 pm to 7 am, shift work is labeled permanent evening and permanent night work, in the second instance working hours alternate between at least two different shifts and this is labeled rotating shift work. Rotating schedules can involve two or more (often three) types of shifts, in most instances covering

also the day shift. Contrary to this perspective, from the organisations point of view, a schedule is considered as a way of organising work *coverage*, regardless of the type of shift work. A continuous operation may this way be covered by fixed shift staff or by rotating shift workers without any real difference for the organisation or employer. The focus of this thesis is the shift work of individuals.

In industry shift work is traditionally done in teams, groups of workers having the same shift schedule. One type of shift in this area is the traditional 5 day shift, 2 days off, 4 evening shifts, 3 days off, 4 night shifts, 3 days off. The schedule can be written DDDDD-- /AAAA--- /NNNN---/[1]. This way three teams could cover a continuous operation from Monday morning to Friday at noon. If a longer operation is desired, for instance by including the weekend, more than three teams would be necessary. In the above example the schedule is three weeks in length, in the fourth week starting over with the day shifts. The teams would work one week delayed from one another. A schedule not including work in weekends is labeled discontinuous shift work.

In other parts of society shift work is by tradition done in more irregular types of schedules, examples being the transportation and the hospital care sectors. Here shift work is often not done in teams but instead every employee have their own schedule.

Relating to the problems of defining shift work the number of shift workers in Denmark is not known. Recent publication rates between 9%²¹ and 18%²² as shift work-

[1] Throughout the thesis I use the notation "D" for day shift, "A" for afternoon shift (evening), "N" for night shift, "--" for day off and "/" to mark the beginning of a new week (sunday/monday)

ers. This is somewhat lower than figures from other Western countries²³⁻²⁵, where 25-30% are reported shift working. The need of shift work is relating to technical, economical and service obligations, of which the first may explain the lower Danish figures. Both of the latter reasons (for instance work organisations like “production on demand”, where stock is being held at a low level requiring flexibility and the increasing use of “around the clock” opening hours of shops) explains why shift work seems to increase. There are no Danish figures, but in Sweden the proportion of the work force with night shift work has doubled in 15 years²³.

12-hour shifts, dividing the day in two, is becoming more and more popular in the United States and is also making its way into Denmark. Besides the problems of shift work it also brings along problems relating to long working hours²⁶⁻³¹ but this is not covered directly by this thesis.

Shift work and health

By displacing the working hours, shift work potentially affects the spare time and family life of all shift workers. The shift worker may experience positive social effects of shift work, for instance when two spouses can take turns looking after smaller children at home³². Most shift workers regards the social impact as negative. Shift work that include night work always leads to circadian disruption (see p. 15) and thus to physiological changes.

In short, evening working hours is mostly related to social and domestic problems, and night working hours to physiological problems. Theories for the mechanisms of this is dealt with in a later section (p. 14). The resulting negative outcomes falls in four categories^{1,11}

- C problems with sleep and sleepiness³³⁻³⁵, eventually leading to effects on performance and higher risk of accidents (at work or while commuting)³⁶.
- C Social disruption with problems relating to the interaction of work and social (family and spare time) life³².
- C Risk of adverse pregnancy outcomes as preterm birth, small for age and prolonged waiting time for conception³⁷⁻³⁹.
- C Disease. This covers psychological distress and maybe psychiatric disease as depression^{40,41}, gastrointestinal disorders and disease^{1,42-44}, and heart disease. The thesis will only cover the last of these items.

Heart diseases

The term "cardiovascular disease" (CVD) comprises ischaemic heart disease, cerebrovascular diseases and diseases in larger arterias and veins, especially in the form of claudicatio intermittens.

Ischaemic heart disease (IHD) or coronary heart disease (CHD) comprises myocardial infarction (MI), angina pectoris (AP), sudden death, cardiac failure, and cardiac arrhythmias⁴⁵. MI is a regional infarction in the heart on the basis of an occlusion of the coronary arteries. AP is attacks of sudden severe chest pain caused by inadequate perfusion of a part of the myocardium relative to the metabolic demands. Coronary Artery Disease denotes coronary arteries affected by a pathological process, and is often thought of as preexisting IHD by many years. While the review (publication I) included CVD broadly, this thesis will primarily relate to IHD.

The pathological processes leading to IHD can be divided in two. The forming of an atheroma in the coronary vessels, and the

secondary forming of a clot leading to ischemia. The atheroma forms in the tunica intima of the wall as a pocket with cholesterol, cholesterol-esters and other lipids being the fat-containing nucleus. Migration and proliferation of smooth intimal muscle cells, collagen, eventually hydroxyapatite and dead cells forms the plaque. The atheromatous plaque produced in this process can lead to a narrowing of the artery lumen, which diminishes the coronary artery flow, eventually leading to AP.

IHD is secondly attributable to the formation of a clot often on the basis of a ruptured or ulcerated atheromatous plaque, and leading to a sudden thrombosis of the lumen.

Heart disease epidemiology

IHD is uncommon below the age of 40 and is more prevalent among men than women before menopause. After menopause, women have the same incidence as men. The gender difference has been related to the protecting effect of endogenous estrogens.

In Denmark approximately 16,000 deaths yearly are attributable to IHD, notably MI and sudden death, and 100-150,000 suffer from IHD (mostly MI and AP)⁴⁶.

In the last decades incidence and mortality of IHD has been declining⁴⁶⁻⁴⁸. Some of the decline has been related to a better prognosis and consequently a lower lethality, but it also seems as if the incidence of new IHD is falling^{46,49}.

Risk factors for heart disease

Since the late 1940's explanations for the development of IHD and detection of people at elevated risk of IHD have been pursued⁵⁰. It was shown that the risk of IHD could be predicted on the basis of conditions in clini-

cally healthy people, and these conditions were labelled risk indicators or risk factors. Although some advocate the use of the term risk factor for situations that predict risk^{51,52}, others have suggested that the term should be reserved for factors that are *causally* connected with the evolution of disease, while the term risk *indicators* could be used for factors that were just associated with IHD⁵³. I use it in the latter meaning. More than 300 risk indicators have been described^{54,55}. Most of these are only proxy measures of other underlying risk factors, and the number of risk factors are probably lower. On the other hand, risk factors discovered until now have only been able to explain half of the changes in incidence, both in individuals and in populations⁵⁶.

Traditional risk factors

Hypertension, diabetes, smoking and hypercholesterolaemia are labeled modifiable traditional risk factors⁵¹. Other conditions have moved from indicator to factor status as more knowledge has been gathered, and lack of exercise, overweight and a J- or U-shaped curve for alcohol consumption are now added as lifestyle related risk factors^{51,57}.

Other risk factors

Among the enormous number of risk factors, only a few - relating to the papers and this thesis - will be discussed.

Social class

Social class can be measured in many ways, but will most often encompass either measurement of some kind of social prestige (normally education) or control with production⁵⁸, or both. In Denmark the scale of Svalastoga⁵⁹ has been used in a revised ver-

sion combining information on education and the number of subordinates⁶⁰. In this scale, social class I encompass self-employed with more than 20 employees, people with longer educations and civil servants with more than 51 subordinates, class II covers self-employed with 6-20 employees or a middle-long education and civil servants with 11-50 subordinates, social class III encompass self-employed with less than five employees and civil servants with 1-10 subordinates. Social class IV encompass civil servants without subordinates and skilled workers, and social class V covers unskilled workers.

A large number of studies showed social class to be strongly inverse related to IHD⁶¹⁻⁶³. The possible causal effect of social class on IHD is not known. The social class term is in some instances a proxy for other risk factors being more prevalent among lower social classes. It has been shown, however⁶⁴, that social class acts as a independent risk factor, not explained by differences in other risk factors. One possible risk factor that social class could be a proxy of is life style, as smoking and a diet rich in saturated fat has been shown to be more prevalent in lower social classes. It has also been suggested that people in lower social classes don't quit smoking and that prevention campaigns do not have the same effect among those. Besides lifestyle factors, the effect of social class has been related to material conditions, selection processes, cultural differences and effects in utero or infancy⁶⁵⁻⁶⁷. The differences in work environment has also been suggested⁶⁸ to be partly responsible, but the work environment in general is only explaining a minor part of the risk⁶⁹.

So, even when control of smoking and dietary habits between shift and day workers is made, this would not necessarily outbalance the confounding effect of social class.

Work environment

A number of work environment factors have been shown to relate to the risk of CVD. Sedentary work has been known since the early 1950, when Morris compared bus drivers and conductors, and later on monotonous work, passive smoking, noise, heat and cold have been included¹³. Occupational stress is discussed on p. 12. Also different chemicals are cardiotoxic⁷⁰ most known is carbondisulfid shown in a series of well conducted epidemiological studies⁷¹. Olsen and Kristensen⁷² calculated the attributable risk (etiological fraction) of work environment risk factors on the risk of CVD to be around 20% that is that 1/5 of CVD cases would not exist if all work environment risk factors were entirely removed.

Personality factors

IHD has been associated with the so-called type-A personality, persons being competitive and with what has been labeled coronary-prone-behaviour, but it has later been shown that it is the hostility and aggression components that are related to IHD^{51,73} and to atherogenic lipids⁷⁴.

Biochemical risk factors (biomarkers)

Morbidity and mortality of IHD is the end point of concern. In order to obtain information on risk at an earlier stage, considerable interests have been on the possible use of biochemical factors as cholesterol and lipoproteins as proxy measures of later risk.

Apart from serving as markers of apparent disease when they are high - as hypercholesterolaemia - the levels of biochemical substances included in the disease process is of importance. There is a dynamic equilibrium of proteins and lipoproteins between the

blood and the arterial wall, especially for the small high density lipoprotein (HDL)-cholesterol and medium-sized low density lipoprotein (LDL)-cholesterol. It is thought that the concentration of for instance LDL-cholesterol in “normal” levels is connected to the progression of disease so that the transport of lipids into the vessel wall will be related to the concentration of LDL.

As the concentration of these biochemical factors represent early, subclinical adverse health effects they can be regarded as biomarkers⁷⁵. I use this notion to separate what is regarded as internal biological effects from external behavioral risk factors. As noted above, the traditional nomenclature would label the biomarkers as risk factors.

Markers of atherosclerosis

The blood lipids cholesterol and triglycerides are in different concentrations integrated in lipoproteins of different densities.

High total-cholesterol and LDL-cholesterol (especially its oxidized form⁵⁴) and low concentrations of HDL-cholesterol have been shown to be causally related to risk of IHD^{51,76,77}.

It has been debated, whether high triglycerides are a causal risk factor, and the level is probably not linearly related, but may be dependent on HDL-cholesterol levels^{51,78}.

In subjects without other risk factors, atherosclerosis is normally not present when cholesterol < 3.5 mmol/l, LDL < 2.5 mmol/l, triglycerides < 1.5 mmol/l, and HDL > 1 mmol/l.

It has been suggested that total cholesterol/HDL-cholesterol ratio is especially useful as a predictor. The ratio should be lower than 5⁵².

The risk factors and biomarkers are interde-

pendent, and this may explain why for instance Japan has a much lower incidence of IHD despite a high proportion of smokers, due to a low level of cholesterol⁷⁹.

These biomarkers are influenced by gender and age and of life style factors. Females have lower total cholesterol, LDL-cholesterol and triglycerides, and higher HDL than men. The relation to the other factors are shown below

	TC	HDL	LDL	TG
higher age (until 55)	>		>	
Saturated fat	>		>	
Carbohydrates		?		
Obesity		?		>
Exercise		>		?
Smoking	>	?	>	>
Alcohol		>		>

Table 1: Relation between risk factors and biomarkers of IHD (adapted from⁸⁰). TC=total cholesterol, TG=triglycerides

A 1% reduction in total cholesterol has been associated with a risk reduction for IHD of 2-3%⁷⁶, a 10% reduction in cholesterol to 20% reduction in IHD⁵², and a reduction of 0.6 mmol/l at any point on the scale to a 50% reduction at age 40, a 40% reduction at age 50 etc⁸¹.

As a high blood glucose has been related to higher risk of IHD, glycated hemoglobin (HbA_{1c}, see also p. 13) that mirrors the blood-glucose concentration in the preceding months also act as a marker of atherosclerosis risk⁸².

Markers of hemostasis

When an atheroma is formed the second step is the formation of a clot. This is regulated by the hemostatic balance.

The end point of the coagulation system is the generation of an enzyme (trombin) that converts fibrinogen into the gel-like fibrin, and thus gives hemostasis. The fibrinolytic process, on the other hand, activates plasmin that turn fibrin into soluble degradation products⁸³ dissolving the clot.

Markers of this delicate web are numerous for among others fibrinogen, tissue-plasminogen activator inhibitor (t-PAI) and factor VII there is knowledge to designate a high concentration as causally related to IHD^{51,54,84-87}. Also other markers of the coagulation and fibrinolytic system (trombocytes, platelet aggregation⁵², factor VIIc^{88,89}, t-PA⁵¹ and complement⁹⁰) are suspected to be causally related to IHD.

Fibrinogen is - like the lipids - affected by diet, tobacco, exercise and obesity⁸⁵.

Triglycerides are supposed to be a stronger and cholesterol a weaker predictor of risk in women than in men⁷⁷, and the hemostasis and insulin regulation is also acting differently in women⁵¹.

Stress and heart disease

Definition of stress

The word “stress” has a variety of definitions but 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” (Lazarus and Folkman⁹¹, p. 19). This interaction is characterised by being unpleasant and tense, and contains both emotional, cognitive, behavioral and physiological components. In this viewpoint stress is an individual and relation-

nal phenomenon implying that people can react very differently to the same stimuli.

Conditions in the work environment can be sources of stress (in other definitions labeled as stressors)⁹²: physical surroundings (light, heat, noise), new technology, quantitative and qualitative demands, lack of goal, unclear roles, conflicts, insecurity, lack of participation, unemployment etc.

In relation to IHD occupational stress have mostly been examined in two distinct models. In the Karasek-Theorell model⁹³ quantitative demands and decision latitude is making up a two dimensional plane, in which both self reported and “objective” scores can place the individual. The quadrant with low control and high demands is labeled “strain” and is especially stress inducing. The model has been expanded with the inclusion of social support as a third dimension and with isolation-strain as the most stressful situation in this three dimensional model⁹³.

More than 20 studies, mainly finding a link between strain and IHD have been published 94-96. Recently, several studies have pointed at control as the important factor⁹⁷.

Another model, the effort-reward-imbalance model (ERI), has been proposed by Siegrist et al.^{98,99} stating that the demands of work are outbalanced by rewards, among others money, promotion aspects and esteem. If people have certain personality traits (previously labeled “immersion”¹⁰⁰, now “overcommitment”), a perceived imbalance between the two are particularly stressful.

Stress as defined by this model has also been shown to be a risk factor for IHD^{100,101}.

Also a few of the other occupational factors have been connected to IHD, especially a noisy environment¹³.

Biomarkers of stress

In situations taxed by the individual as stressful, an acute release of epinephrine, norepinephrine and a more slowly release of cortisol is made¹⁰². This gives as an effect a release of glucose and free fatty acids, used as “fuel” in the “fight or flight” reaction.

The effect of acute stress can be measured by epinephrine, norepinephrine and cortisol but neither of them are well suited for field experiments because diurnal measurements are needed¹⁰³ and the half-life in blood is minutes to hours¹⁰⁴.

If the situation anticipated as stressful continues a change in the release of hormones are seen. In a chronic strained person anabolic hormones such as testosterone, dehydroepiandrosteron and estradiol are depressed. Other anabolic functions and the immune system are also lowered.

Stress has been shown to alter lipid levels in non-laboratory situations, but eventually only the more severe forms⁷⁴ for chronic stress mostly studied in relation to demands and control and to job insecurity. Only few studies have found a relation⁷⁴ although another review found that stress may bring about a rise of 25% in cholesterol¹⁰⁵. One explanation might be that the *perception* of threat in the situations hardly ever is evaluated.

Triglycerides has been proposed as a indicator for stress as epinephrine mobilizes free fatty acids¹⁰⁶.

Clotting factors have been shown to be related to stress among tax accountants increasing blood coagulation¹⁰⁷, but the literature in general does not agree whether stress is related to clotting factors¹⁰⁴

Because stress is followed by higher blood glucose, glycated hemoglobin as an integrated marker of blood glucose for the previous 1-2 month (corresponding to the half-life of

erythrocytes) will be higher as a marker of the metabolic regulation 108¹⁰⁹. Also other glycated proteins as glycated fructosamin could be used 110¹⁰⁴.

Prolactin has in several studies by Theorell et al.^{111,112} been shown to increase in stressful encounters, especially when the person is powerless and passive (compared to being in command and active) or responding to the stressful encounter with passive coping.

The stress response may, however, be more complicated than outlined. The body seeks to maintain equilibrium and changes may be leveled out leaving surprisingly steady concentrations despite high stress levels¹⁰⁴. From this point of view biomarkers not part of the metabolic equilibrium itself may be more steady markers (eg. HbA_{1c}).

Shift work and CVD

Epidemiological evidence

The epidemiological literature on shift work and CVD has been reviewed in publication I. It examines 17 studies (including publication II) and it suggests that shift work is associated with an increased risk of CVD. The best available estimate is a relative risk of 1.4 from the study by Knutsson in 1986⁷ and supported by other studies of different methodology. Some studies were not included in the review due to a demarcation to English or Scandinavian publications with comparisons between day and shift workers. A German review¹⁷ included 8 studies in the German language. One study was excluded for comparing three and two shift workers¹¹³, and one study because it was not clear whether the control groups was in fact day working¹¹⁴. [2]

[2] Two reviews on shiftwork and heart disease have been published since publication I:

Among the 17 studies included in the review some did not find an association between shift work and CVD. This prompted a further and deeper study of the literature¹¹⁵. In a meta-analytic approach of the 17 studies we identified two groups of longitudinal studies with individual exposure classification, one consisting of four “positive” studies, and one of five “negative” studies (table 2). As the basic idea of a meta analysis is that the included studies should be measuring the same relationship between well defined exposure and outcome, this is probably not fulfilled - as is often the case in meta analysis of observational studies. The chi-square test of heterogeneity is not very powerful, but the result suggests that at least two different groups of studies are present.

Group of studies	OR _{meta} (95% CI)	P ² (p-value)
“positive” ^{116;7;117;118}	1.31 (1.17-1.45)	0.26 (0.97)
“negative” ^{119;120;121;4;(II)}	0.96 (0.85-1.08)	2.06 (0.72)

Table 2. Meta analysis of longitudinal studies of shift work and IHD with individual exposure classification. Aggregated odds ratio with 95% confidence intervals (CI) and a chi-square test of homogeneity with n-1 degrees of freedom. (From¹¹⁵)

We further tried to identify study charac-

Steenland K. Shift work, long hours, and cardiovascular disease: a review. In: Schnall P, Belkic K, Landsbergis P, et al, eds. *The workplace and cardiovascular disease (Occupational Medicine: State of the Art Reviews)*. Philadelphia: Hanley & Belfus, Inc., 2000:7-17

Dong W. Shift work and cardiovascular disease. *Israel Journal of Occupational Health* 2000;**4**:33-38
Neither adds substantially to the knowledge (appended July 2000)

teristics that influenced the meta-regression analysis. This only suggested that studies with an aggregated exposure classification gave higher risk estimates than studies using individual exposure classification. This was not anticipated.

Mechanisms

Several models have been proposed to explain the relation between shift work and health^{16,122,123}, mostly suggesting a web of causes. None of the models have been dedicated to explain the risk of IHD.

The other part of the review (publication I) discussed possible explanations for a causal relationship between shift work and heart disease. Expanding the model proposed by

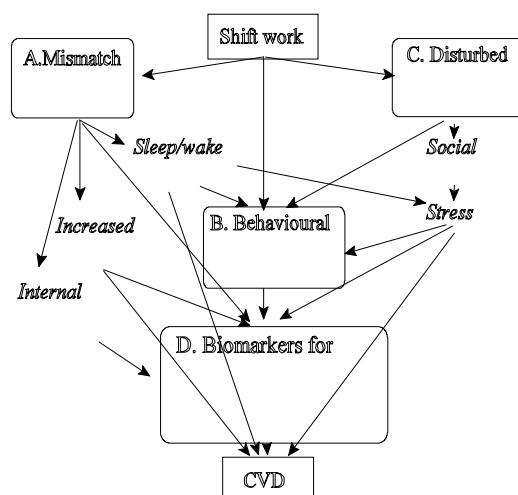


Figure 1. A possible causal web between shift work and IHD. Width of arrows are not related to importance

Knutsson¹⁶ we suggested four possible interactive mechanisms as part of a causal web and identified studies that had dealt with these (see figure 1)[3].

[3] An updated version will appear: Knutsson A, Bøggild H. Shiftwork and cardiovascular disease:

A (see figure 1): Most of the functions in the body has a rhythm during the day, so that for instance concentration of hormones and lipids, temperature, hand grip strength, airway narrowing etc. each day follow their own pattern (figure 2). These biological and psychological *circadian*[4] *rhythms* are driven by an autoregulatory genetic clock¹²⁴ in the suprachiasmatic nuclei of the hypothalamus¹²⁵ and exists even in dark caves where no *zeitgebers*[5] as the dark/light pattern are present. The robust clock which in most individuals runs at approximately 25 hour is synchronized to the 24-hour external environment by entrainment of dark/light pattern, watches, social activities etc. Melatonin released from the pineal gland may act as the internal messenger¹²⁶.

When working at night and sleeping during day these circadian rhythms move but even after weeks of night work no complete adjustment of the rhythms are made¹²⁷. The single rhythm moves at its own pace and

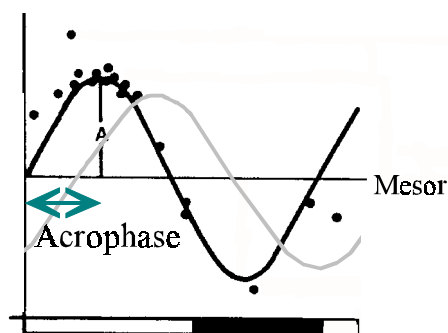


Figure 2. Circadian rhythm fitted in measurements. A hypothetical desynchronisation with a phase-delay of 3 hours is shown in grey. A=amplitude

review of disease mechanisms. *Reviews on Environmental Health* 2000; (in press) (appended July 2000)

[4] From Latin: circa dies, around 24 hours

[5] From German: time signal

several rhythms may come in disharmony with each other or the surrounding. This is labeled *internal desynchronization*^{35,128}.

In a rhythmic function the *acrophase* describes the timing of a rhythm in relation to a reference time point, representing the crest of the cosine curve best fitting the data (see figure 2). The *mesor* is the midline estimating statistic of the rhythm, being the value midway between the highest and lowest value of the curve best fitting the data. The *amplitude* is the distance between the mesor and the highest point on the fitted curve¹²⁹.

Also factors relating to the cardiovascular system follows circadian rhythms^{130,131} and may be desynchronized during night work. Some factors (like blood pressure) are primarily externally influenced for instance of activity¹³² but the rhythm is still controlled by the internal clock, this external influence called *masking*. In some¹³³⁻¹³⁶, but not all¹³⁷⁻¹³⁹ of the studies on night shift work and blood pressure, a longer plateau of high systolic pressure is described in the night rhythm.

It has been shown that also lipids have a circadian rhythmicity, and in day orientation the circadian variation (given as percentage of the total variation) was 5.6% for HDL/total cholesterol ratio, 30.5 and 31.6 for HDL and total cholesterol, 33.5% for LDL and 38.5% for triglycerides¹⁴⁰ (see figure 5). These circadian rhythms follow a primarily endogenous circadian rhythm¹⁴¹, with triglycerides having the acrophase early in the morning, the others later in the day. Fibrinogen peaks in the morning with a 10% amplitude¹⁴². t-PAI has its acrophase at 3 am with an amplitude of 50%¹³¹. Protrombin (factor II-VII-X) seems to be lowest at night (although the results are conflicting)¹⁴².

There is also a yearly rhythmicity, cholesterol and LDL-cholesterol being up to 3-5%

higher in winter (cold period), while HDL and triglycerides are only modestly changed⁸⁰.

Several studies in the last years have examined the influence of meal timing on the postprandial levels of lipids and glucose. In one study the postprandial response were lower for cholesterol-rich lipoproteins at 1 am compared to 1 pm, while the response of triacylglycerol-rich lipoproteins were higher at night¹⁴³. In another study the insulin response was found to change during night eating¹⁴⁴, but not replicated in a new study by the same group¹⁴⁵ using a different diet. These studies suggest that the timing of food intake may influence the metabolic function.[6]

The amount of carbohydrates ingested in the night hours was associated to cholesterol levels¹⁴⁶, and it was suggested that this was due to an internal desynchronisation between eating and metabolism.

The literature on shift work and desynchronization in relation to IHD is very fragmented with only very few studies available (I). On the other hand there is indications to believe that this pathway may be important.

B) Shift work leads to changes in lifestyle, for instance in relation to diet, smoking, alcohol and exercise, all being risk factors of IHD. The literature shows that changes in for instance smoking habits must be very slow¹⁴⁷, with shift workers followed for ½ year not

beginning to smoke[7]. Furthermore, smoking may be viewed as a way of coping with the stress of shift work. Lifestyle changes may also be more directly influenced by the shift work, as for instance cantinas may be closed at night¹⁴⁸ leaving little possibilities for better nutrition.

Most of the literature on shift work and IHD have concentrated on lifestyle (I), and we concluded that shift workers smoked more and ate more irregular than day workers, while exercise and alcohol consumptions were not affected by shift work.

C) The interaction between work and family life may lead to stress. Shift workers have to sleep in the day time, may be unavailable for the family in weekends, and may have problems in attending regular social arrangements, such as evening school. Sleep is often compromised for both physiological and social reasons and may be compromised when shift workers choose between family time and sleep.

Several studies¹⁴⁹⁻¹⁵³ have suggested two major contributors of stressfull experiences in shift work:

- C Physiological disruption of circadian rhythms, leading to sleep problems, fatigue and exhaustion.
- C Social conflicts, as working hours in evening and night collide with family interactions.

[6] In a recent study (Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;**354**:1435-9) it was shown that sleep deprivation (4 hours/day for 6 days) gave a 40% decrease in glucose tolerance. (appended july 2000)

[7] However, in a recent study (van Amelsvoort L. *Cardiovascular risk profile in shift workers: cardiac control, biological and lifestyle factors (thesis)*. Wageningen: Grafisch Service Centrum Van Gils B.V., 2000:1-131) 81 smoking shift workers starting on a new job smoked 2.4 cigarettes more after one year of follow up. It was calculated, that it would increase the risk of IHD with 10% over 20 years. (appended july 2000)

The identified areas have not been associated with empirical data, but is mostly based on knowledge of the effects of shift work in general and on theoretical considerations.

The strain of shift work is this way tied to other factors than normally examined in work related stress. The shift workers may moreover be subjected to the same stressors as other workers, for instance in relation to monotony, high demands/low control or noise, and it has been theoretically argued that the shift worker may be more sensitive¹⁵⁴.

Neither social strain nor sleep problems have been tied to IHD in shift work (I)

Recently a couple of studies have examined stress in shift workers in relation to IHD.

The articles have been using the demand-control model of Karasek and Theorell, finding no difference between shift and day-workers¹⁵⁵ or the Effort-Reward-Imbalance finding that imbalance had an influence on the association between shift work and hypertension but not with lipids¹⁵⁶.

In a couple of studies of shift work and IHD demand-control measures have been used to control for stress^{117,118}. In the Helsinki Heart Study shift workers had lower control but the same demands as day workers, also after controlling for social class (own reanalysis).

D) Biomarkers of stress and IHD could be the link to disease, the literature finds shift workers in general to have higher total cholesterol, triglycerides, and a slightly higher blood pressure (I). Markers of hemostasis and stress have not been dealt with, except for one study using HbA_{1c}. These shift workers were, however, also exposed to other stressors (noise, overtime)¹⁵⁷.

As stated, the focus of the literature has been on lifestyle factors, and almost no studies have examined the other two suggested major pathways, circadian rhythmicity disruption and stress as a consequence of lack of sleep and social disruption (I).

Since the review, another three studies on shift work and blood pressure have been published^{135,138,158}, Morikawa et al finding a higher risk of hypertension among young shift workers in a cohort design.

Two new possible explanations for an association between shift work and IHD have been put forward since the review:

In an analysis of cross sectional data from the Swedish WOLF study¹⁵⁹ shift workers have been shown to have higher prevalence of the “metabolic syndrome”, a collection of symptoms and signs related to the metabolism, which is also a risk factor for IHD. The analysis comprised 734 shift and 855 day workers. Shiftworkers had a higher prevalence of triglycerid above 1.7 mmol/l, lower HDL-cholesterol, higher waist-hip-ratio (WHR) but no difference in BMI. Shift workers had lower prevalence of hypertension. The shift workers had more often several risk factors present than day workers. The higher WHR has also been reported in a cross sectional sample of Japanese shift workers⁸⁶.

In two studies from the same Japanese group, cross sectional¹⁶⁰ and longitudinal data¹⁶¹ show shift workers to have a prolonged -QTc-interval on their ECG, which has been shown to raise the risk of CVD. In the longitudinal study¹⁶¹ 158 blue collar shift and 75 white collar day workers were followed for 10 years. HDL, triglycerides and blood pressure did not differ. At baseline, shift workers had already prolonged QTc, but among those with normal QTc (<420 m/s(1/2)) more shift workers had a prolon-

ged interval after 10 year.[8]

Individual modifying factors

Shift workers may react very differently to the shift work exposure. A variety of personality factors have been proposed to influence whether a shift worker will be able to cope with working hours. The factors suggested to lower adaptation to shift work include neurotism, introversion, lack of hardiness and sleep patterns (rigid sleep, morningness (lark))^{162,163}. Besides this age, experience with shift work, an individual circadian variation, the experience of having chosen shift work, and satisfaction with work have been related to successful adaption to shift work. Outer factors, such as possibilities for employment, risk of unemployment, motivation, work load, challenges in work, housing (ability for sleep), transportation etc may also influence the ability to cope with shift work^{154,164}. The effect of these differences has not been related to IHD.

The individual dimension in the stress reaction makes people react differently to the same stimuli. If, for instance, noise is expected and with a function for the individual the body reacts differently than if the noise is unexpected and without a function^{165,166}. This may parallel shift work where problems with work-family life interactions may be accepted due to economical incentives, and shift workers that feel they volunteered to shift work

may act differently than those feeling shift work to be forced upon them. It has, however, not been examined.

Gender difference

In relation to stress, it has been shown that gender differences exist in the cognition of stress reflecting both biological (metabolic) and social differences being present between men and women¹⁰². Males have a rewinding of the stress hormones after going home from work, while females have a persistent high concentration because of the responsibility to look after the home. Also female shift workers experience more responsibility for child care and often have a more fragmented sleep^{167,168}. In the epidemiological literature the risk of IHD for female shift workers is in the same magnitude as for men (I).

Shift scheduling and prevention

Within the framing of a shift schedule, that is the number of workhours covered, the number of persons needed at different hours et cetera the schedule can be made up quite differently. The schedule may more or less take circadian disruption and social/family life - work conflicts into account.

Danish legislation offers no direct help in drawing up schedules. The law¹⁶⁹ only states that workers (regardless of being shift or day workers) should have at least 11 hours off in every 24 hour span, and a full 24 hour off in connection with the 11 hour daily rest period once every 7. day. Both periods may be postponed until respectively 8 hours of daily rest and a rest day every 11. day. This is normally done after consultation with union representatives. The EU-directive on working hours¹⁷⁰ did not change these constraints.

Unions have agreements with regulations

[8] A third possible explanation was recently proposed by van Amelsvoort (van Amelsvoort L. *Cardiovascular risk profile in shift workers: cardiac control, biological and lifestyle factors (thesis)*. Wageningen: Grafisch Service Centrum Van Gils B.V., 2000:1-131). Shift workers had more ventricular extrasystoles in 24-hour Holter monitoring after one year of follow up than day workers, mostly so in workers having > 5 night shifts a month. (appended July 2000)

concerning for instance the mean number of hours worked a week, but normally no constraints on the shift schedule are given. So there is very wide opportunities to schedule shift systems.

It has been discussed what type of shift system that would lead to the least strain. There is no universal agreement¹⁷¹⁻¹⁷³. The prevailing European view has been to keep circadian rhythms as close to day orientation as possible, while Americans have suggested very long spells (months) of night shifts in order to allow the circadian rhythms to synchronize to night working. A problem in the American tradition is that even permanent night shift workers maintain a day oriented life at days off, allowing the circadian rhythms to a rapid synchronization with day orientation. In a recent publication from NIOSH¹⁷⁴[9] the European view has therefore been adapted

Several studies have shown day sleep to be longest and best in slowly rotating and permanent systems^{171,175} and permanent shift workers have more often the feeling of having choosed to work at night¹⁷⁶. There is only limited knowledge of the effect of permanent shift work and IHD. In an aggregated study permanent night shift was found to have the same risk of hospitalization as rotating shift¹⁷⁷.

Ergonomics and shift schedules

Several groups have evolved ergonomic criterias for shift scheduling with the aim of minimizing the adverse effect of shift- and night work^{174,178-181}. It is important to notice that the criterias are predominantly based on physiological and circadian knowledge although social factors are also covered. The

criterias may be in conflict with each other. Different European proposals do not differ much, and one of the most widespread list is from the BEST-group¹⁸¹, suggesting 14 criterias. They are:

- C Minimise permanent nights
- C Minimise sequence of nights (to 2-4 night shifts in succession)
- C Avoid fast double backs (with a short time off between two shifts (e.g. 8 hours))
- C Plan rotas with some weekends off
- C Avoid overlong work sequences (compressed working weeks; 12 hour shifts)
- C Fix shift length to task loads
- C Consider shorter night shifts
- C Rotate forwards (e.g. morning shift, then afternoon, then night)
- C Delay morning start (to after 7 am)
- C Allow flexibility in shift change times
- C Keep rotas regular (for planning a normal life)
- C Allow some individual flexibility
- C Limit short-term rota changes
- C Give good notice of rotas

Rota risk profile analysis (RRPA)

There have been a number of papers on algoritms for evaluation of shift schedules on ergonomic principles^{182,183}, but no common accepted way of doing it. Some of the algoritms have been translated to computer programs. Besides the inventors own use no formal evaluation has been made of their appraisability and no comparison between the algoritms or programs. Other computer programs have been written that can help *designing* ergonomic better schedules¹⁸⁴.

[9] National Institute of Occupational Safety and Health

The Rota-risk-profile-analysis (RRPA) by Jansen et al.¹⁸⁵ computes nine scores for different schedule characteristics. The basic features of a schedule are keyed in the program. These include types of shifts (day, evening, night etc with start and stop hours) and the actual schedule. The calculation of a schedule results in two types of scores, one basic score ranging from 0-10, with 0 for bad and 10 for excellent. The basic score is calculated as a mean of all weeks in the schedule, and a constancy score provide a figure that is high if the weeks in the cycle are alike and low if the weekly scores are very different. The constancy score range from 0-100. The combined score is then calculated as basic score - (100-constancy score)/100

The scores and their definition have been gathered in table 3, p. 22.

Eventually, the program calculates mean working hours/week, operating time, working hours between 22-06 in rota, the number of times with less than 11 hours between shifts, the number of times with less than 36 hours rest between blocks of shift, and the number of sundays off in the rota.

The scores depend heavily on the assumptions in calculations and in some instances other values could have been selected (the number of night shifts in a row is for instance reflected in the PE (cumulating circadian disturbance) and could be valued higher). The benefit of the RRPA, however, is that the schedules are summarized in a variety of scores in a meaningful and “objective” manner.

Intervention in shift scheduling

Harrington¹ stated that “surprisingly few [scientists] have tried to evaluate new rotas before, during, and after, introduction” (p.3). 20 years later this is still so, at least if inter-

ventions are seen as planned and applied activities, designed to produce designated outcomes¹⁸⁶. Most intervention studies in the area still seems to be coincidental in design, being made when shift schedules are changed at management decisions, and not from a theoretical idea, followed by a change in schedule. Furthermore, several intervention studies lack a control group¹⁸⁷⁻¹⁸⁹, which gives the possibility for a Hawthorne effect that the interest itself is capable of producing a positive outcome, regardless of its content.

Most of the controlled studies are either examining a change from counter clockwise to clockwise rotation^{18,187,190}, a reduction in the consecutive number of night shifts^{189,191,192} or a change towards permanent night shift work^{188,193}.

A couple of studies are examining several changes simultaneously, including both a change in the direction of rotation and in the number of consecutive night shifts (from 6-7 to 3-4)^{194,195}, a change towards permanent combined with forward rotation¹⁹⁶, an intervention aimed at forward rotation, predictability and participation¹⁹⁷, or faster rotation, extra day off after last night shift and fixed evenings off¹⁹⁸.

In general, satisfaction in all of these interventions were high, although the employee in some instances - despite higher well-being in the new schedule - chose the old schedule, most often due to longer spells of days off^{18,197}. In most instances the change led to better sleep quality^{187,188,191,194,196,197}, while symptom scores in general did not change.

Shift intervention and biomarkers

Two studies have evaluated certain characteristics of ergonomically scheduled shift systems in relation to biomarkers of

heart disease.

Orth-Gomér¹⁸ followed 46 male police officers. In a cross-over design, half of the men were first followed in clockwise rotation for four weeks, then counter-clockwise for another four weeks. The other group worked vice-versa. Sleep quality was better at clockwise, but with no difference in symptom scores, smoking pattern or self reported physical and psychological strain. There was lower irritability at clockwise rotation. There was a change in triglycerides so that values changed toward lower values in the clockwise period and worsened in counter-clockwise compared to the middle period. For glucose lower values appeared in both clockwise and counter-clockwise rotation, but mostly so in the clockwise period. Also systolic blood pressure was lower after clockwise than counter-clockwise rotation.

Kecklund et al.¹⁹⁹ followed an intervention with a change from 7 to 3 and 4 night shifts in a row at a power plant. 72 shift workers were followed during two years, and 48 of these and 15 of 60 day working controls had blood pressure, triglycerides, cortisol and total-, HDL, and LDL-cholesterol measured. Sleep was improved, the social problems were lower, and there was a general satisfaction with the new schedule. In the period HDL rose and LDL/HDL-ratio fell in the intervention group. Also both systolic and diastolic blood pressure fell.

Two other studies with pseudochanges in the shift schedule and measuring of biomarkers should be mentioned:

12 new shift workers and 13 new day workers were examined before starting and after

six month of work¹⁴⁷. All had normal cholesterol and triglycerides. Height, weight, blood pressure, cholesterol, triglycerides, apoB and apoA1 were measured. At baseline the shift workers were younger with a higher BMI and higher systolic blood pressure but lower cholesterol and apo-B than the day workers. During the six month follow up the apoB/apoA-1 ratio rose more in the shift workers, than in the day workers. No other differences were found.

In a uncontrolled study²⁰⁰, 447 workers at a car factory had their schedule changed from two shifts 8-17.30 and 21-6 to a new two shift schedule 6.30-15.15 and 16.15-1.00. Using data from the company medical records with measurements before and after the change it was shown that cholesterol fell from 201.8 to 195.2 mg/dl, HDL rose from 53.3 to 62.2 and triglycerides fell from 109.2 to 98.9. Systolic blood pressure fell from 122.1 mmHg to 116.9 and diastolic from 77.2 to 74.5 mmHg.

These four studies all suggests that the outline of the schedule will influence biomarkers of IHD.[10]

[10] van Amelsvoort (van Amelsvoort L. *Cardiovascular risk profile in shift workers: cardiac control, biological and lifestyle factors (thesis)*. Wageningen: Grafisch Service Centrum Van Gils B.V., 2000:1-131) showed in a one year follow up of 150 day and 227 shift workers that HDL rose and total- and LDL-cholesterol decreased in both groups. LDL/HDL-ratio decreased mostly in shift workers. Also decreases in BMI and WHR were seen in shift workers. (appended july 2000)

Table 3. Rota risk profile analysis (RRPA) scores and their definitions (adapted from Jansen and Kroon)¹⁸⁵

score	description
Regularity (RE)	Changes in work time, frequency and nature 1) number of changes in start and stop hours in continuous shifts 2) the timing of the change 3) changes in start hours are considered twice as difficult as stop hours The changes are linearly standardized
Periodicity (PE)	Extent of circadian disturbance by the schedule 1) weighting the worked hours 2) accumulation over consecutive shifts (no adaptation) 3) correction for direction of rotation (10%) The corrected changes are linearly standardized
Load/shift (LS)	Mean number of hours pr. shift, standardized with a parabolic figure assuming a cumulative effect of long work hours
Load/week (LW)	Mean number of hours pr. week, standardized with a parabolic figure assuming a cumulative effect of long work hours
Opportunity for rest at night (ON)	Mean number of hours worked between 23-07 transformed linearly
Predictability (PE)	A measure of the extent that the schedule can be “mentally” foreseen 1) length of rota in weeks 2) multiplying the number of different shift types and clusters found over the cycle 3) the number of stand-by shifts (maximum 10% of basic figure) linearly transformed. The constancy score depicts the variation in the weeks in the number of shift clusters and the number of different shifts
Opportunity for household activities (OH)	Amount of daytime free on weekdays
Opportunity for evening activities (OE)	Amount of evening time (19-23) on weekdays
Opportunity for week-end recreation (OW)	Number of Saturdays or Sundays with at least 21 hour consecutive hours off. An entire free weekend is multiplied with 2

General aims of the studies

The overall aim of the thesis and the studies presented is to examine whether shift work is a risk factor for IHD. I will use two different approaches; The first (publication II and III) is to address two possible problems in the epidemiological literature, relating to the selection of comparison groups. One is the apparent need for controlling for social class, the other is the possible differences in work environment conditions between shift- and day workers.

If shift work is related to heart disease, then possible causal links between exposure and disease will be needed to explain the association. While these possible links in a causal web is discussed in the review (I) the second approach would be to change the shift scheduling in accordance with ergonomic criterias and examing if biomarkers for heart disease change. If they do, it will add to the credibility of the claim of a causal relation. The second group of publications (IV and V) attacks the problem from this point of view.

A third approach uses all five publications in a discussion of the definition of shift work as an exposure. In the literature shift work is most often used as a bivariate exposure; However, problems relating to this approach and a suggestion of several underlying modalities will be presented. If shift work is causally connected to IHD, then it should be

possible to identify characteristics of the schedule that are more harmful than others.

The aims of the studies are thus to investigate:

- whether shift work is a causal risk factor for IHD, or whether confounding from social class and work environment could be responsible for the association.
- whether changes in shift work scheduling in accordance with ergonomic criterias can lead to lower biomarkers of IHD
- how different shift work exposure definitions might influence the biomarkers of IHD
- whether stress can be responsible for the relationship.

As the modern society is based on workers being on shift, and as shift work is therefore not avoidable, the demonstration of lower biomarkers for IHD after an intervention and the possible identification of schedule characteristics related to biomarker levels would leave potential possibilities for prevention through shift work scheduling.

This would be the ultimate goal of the work being done; to show ways of lowering a possible shift work induced risk of heart disease among shift workers.

Material and methods

Publication I

Publication I reviews the shift work literature both on the risk of CVD and on possible causal mechanisms. The literature was found through Medline (from 1966) and OSH-ROM, and we handsearched the proceedings from meetings in the ICOH Commissions on Night and Shift Work and on Work and Cardiovascular Disease. Eventually listed references from the literature and personal contacts were used. The search revealed 17 epidemiological studies, comparing shift workers with day workers on CVD end-points (mortality and morbidity). The second part of the review used a model to explore the possible mechanisms in relation to known or suspected risk factors, risk indicators and biomarkers.

The review has already been cited in the background chapter.

Publication II

Publication II is based on a reanalysis of the Copenhagen Male Study (CMS). CMS is a prospective longitudinal cohort study, established in 1970 to address physical activity as a risk factor for ischemic heart disease. The participants were examined again in 1985-86. The original cohort comprised 5249 men aged 40-59 in 14 larger companies covering railway, public road construction, military, post, telephone, customs, national bank and medical industries. At the second baseline all survivors were invited, and 3387 participated. In this reanalysis only information on working time was used from the 1985-6 baseline. Information of exposure at both baselines came from a questionnaire, and comprised of shift work, night work and irregular working hours, and of daytime work.

Social class and risk factors (alcohol, smoking, leisure time physical activity, sleep, history of diseases) were also collected from questionnaire, and in a physical examination, fitness value, height, weight and blood pressure were measured.

Information on hospitalisation of IHD and mortality of all causes up until 1993 was found in the National Health Service register and from the Danish Institute of Clinical Epidemiology.

Baseline differences of the shift and day working cohorts were compared with logistic regression models, and the relative risks of IHD and all cause mortality over 22 years were calculated by way of Cox proportional hazards regression models.

Publication III

Publication III is based on a reanalysis of the Danish National Work Environment Cohort Study. In 1990 a sample of 9653 was drawn randomly from the Central Population register, of which 8664 were interviewed. 5940 worked as employees within the last two month prior to the interview. The telephone interview comprised information on a number of working condition. Working hours were divided in four categories, night work and three-shift work, evening work and two-shift, other irregular working hours including morning work, and day work. The reanalysis examined the prevalences of work environment factors, known or suspected to be risk indicators or risk factors for IHD in shift and day workers. The work environment factors examined were length of working hours, ergonomic exposures, repetitive working tasks, dust, heat and noise exposure, walking or standing postures, quantitative and cognitive psychological

demands, decision authority, social support, conflicts at work and job insecurity. Information on social class was also included to examine whether differences were due to social class.

Odds ratio for prevalence of the work environment factors in each of the three groups compared to day work was calculated in logistic regression models, controlling for social class. In order to examine the impact of age, the material was stratified on age in three groups and the models were repeated.

Publication IV and V

Publication IV and V are based on the NAR-FE II-project. It was a longitudinal controlled quasi experimental intervention study among nurses and nurses aides at 10 hospital wards at Aalborg Regional Hospital. The intervention consisted of a change in principles for shift scheduling introducing four principles consisting of more regularity and predictability, a maximum of 3-4 consecutive night shifts in a row followed by an extra day off after last night shift, maximizing the number of weekends off, and a change from three to two types of shifts. Six wards were originally included in the discussion of changing schedules. One ward was divided in two just before the intervention and of the seven wards, four choosed to start scheduling their rotating shift work according to ergonomic principles. Two wards who could not find ways of changing schedule agreed to continue in the project as control wards of the intervention. Among the four intervention wards two introduced all four principles, and the other two only one-three principles. Furthermore, the change only encompassed (some) of the staff having rotating shifts, and not the fixed evening or night shift staff. Four outpatient clinics with day work only, were also included as controls. The staff were

individually approached and gave informed consent to participate in the evaluation.

254 staff members were invited, of which 172 (67.7%) agreed to participate at baseline. At six months follow up, 17 had left the wards and of the remaining 155 nurses and nurses aides, 101 participated at the second data collection. At the intervention wards a third data collection was done after 12 months but participation rate was only 36% (36 ward personnel of 100 at four wards).

The data collection included:

At six of the wards (intervention and intervention control ward), a questionnaire was used in the pre-intervention process in September 1996, with questions on attitudes towards shift scheduling, social factors, and symptoms. These informations were used to evaluate differences between participants and non-participants in the intervention period.

Just before the intervention was put into effect in April 1997, a questionnaire, a requisition for blood tests and a diary was distributed at the intervention and intervention control wards. For a smaller group the material was supplied in May. At the day control wards the material was distributed one year later, in April and May 1998.

The questionnaire was based on the Standard Shiftwork Index²⁰¹, and among others included information on age, having spouse and children, personality factors, sleep type and quality, heredity, moonlightning, attitudes, impact and satisfaction with schedule. The symptom scores included selfrated health, physical health questionnaire, scales on stress, vitality and mental health. Lifestyle factors included exercising, smoking, alcohol, and coffein consumption. Social impact and conflicts were included, as also questions related to commitment with colleagues, work satisfaction, demands, control, and social support at work (for further information on

questions, see publication IV, appendix).

Blood sampling was done between 8 and 10 am at the local Department of Biochemistry by trained bioanalytics, at least three days after the last night shift, and after eight hours of fasting. Analyses included glycated hemoglobin, immunoglobulin A and prolactin as markers of stress, blood glucose to control for diabetes, and triglycerides, total cholesterol and HDL-cholesterol. LDL-cholesterol and total/HDL-ratio were calculated. Fibrinogen, tissue-plasminogen-activator-inhibitor and factor II-VII-X were analysed as markers of thrombosis.

The diary consisted of a double page for each of up to five days, consisting of one day, one evening, two night shifts and a day off. The diary included information on dietary distribution, self reported stress, physical activity, energy, sleep length and sleep quality, means of commuting, and a selfassessment of sleepiness.

After 6-8 months and after 12 months at the intervention wards, a smaller questionnaire, requisition for the same blood samples and the same diary were distributed.

Information in the diary is not used in these papers, as the participation rate was low.

From two eight week periods, one just prior to the intervention, and one a year later, shift schedules were collected from intervention and intervention control wards, and entered into the RRPA computer program¹⁸⁵.

In publication IV data on the intervention effect from the first to the second datacollection period was analysed. Two approaches were employed. In order to analyse according to a "intention to treat"-principle (here: "intention to change"), participants were divided into three groups according to ward and questionnaire data. Participants stating in the second questionnaire that their schedule

was changed due to the project were divided into two groups, according to ward. The two wards that had introduced all four principles comprised one group, and another was formed from the other two intervention wards, agreeing to 1-3 of the four principles. Participants that indicated they did not change shift schedule constituted the reference group regardless of ward, as did the day working outpatient clinics.

The second approach was to analyse changes in the RRPA-scores regardless of whether the participants were intended to have their schedule changed due to the intervention.

In publication V, the baseline data was used to examine relation between different shift schedule characteristics and biomarkers in a cross sectional design. Different shift definitions, including or excluding night work, schedule characteristics as regularity, predictability, periodicity, number of night shift hours worked, part time employment, and number of night, and evening shifts in a row were examined.

The RRPA scores for regularity, predictability and periodicity were divided into tertiles and compared with the lowest values as reference group.

All scales in the questionnaire were subjected to control of the psychometric properties, with calculation of Cronbachs alpha, item-scale correlation and factor analysis.

Nominal scales were compared with the P^2 -test and Fishers exact test, ordinal scales and non-parametric interval scales were compared with Mann-Whitney and Jonckheere-Terpstra tests, and paired data with the Wilcoxon test. For interval scales following a normal distribution linear regression analysis was used, eventually after logarithmic transformation.

In both publications, adjustment was done for age and for lifestyle factors known to be related to the biomarkers (smoking, alcohol and exercise). In publication V some of the regression models also included a step that adjusted for the number of night shift hours worked.

As the outcome in both publication IV and V were correlated biomarkers it was also planned to use MANOVA analysis, but as we were not able to harmonise variance and obtain a normal distribution, this is not presented.

Summary of results

Publication II

Shift work was not associated to all cause mortality or to incidence of IHD. For the whole 22-year follow up, the age adjusted relative risk was 1.0 (0.8-1.2) for IHD and 1.1 (0.9-1.2) for all cause mortality. Controlling for social class did not change these estimates, and further controlling for sleep length, tobacco, age, weight, height, and fitness were not changing the estimates.

Men being shift workers in both 1971 and 1985 had the same risk as ex-shift workers in a eight year follow up from the 1985-6 baseline. Both a skewed distribution of social class between shift and day workers and a social class gradient in the risk of IHD were seen. Social class would, by this, act as a potential confounder. Due to the large group of shift workers in social class III that had an intermediate risk, this heavily influenced the results. When analysing only participants in the outermost social classes, I, II and V, the unadjusted RR was 1.3, which fell to unity when adjusted for social class. Although a distribution of participants like this would be unlikely to be encountered, it suggests that the confounding effect of social class is relevant and should be controlled.

Publication III

In NWECS we examined the correlations of shift work with other working environment factors that might act as risk factors of cardiovascular disease. Compared to day, shift work was associated with shorter working week length, especially in females, exposure to noise (males), heat (males), passive smoking (mostly males), walking or standing postures (females), ergonomic exposures (females), monotony (males), high cognitive (but not quantitative) demands, low decision

authority and skill discretion, and conflicts at work. High quantitative demands were more seldom seen among male three shift workers than day workers.

The only work environment factors not being more prevalent among shift workers in at least one group were dust exposure and quantitative demands. The different types of shift work were associated to different work environment factors.

Especially evening and night shift work were correlated with lower social classes in men, and controlling for social class changed odds ratio estimates especially in males for cognitive demands and conflicts at work.

Publication IV

Publication IV showed that an intervention in shift scheduling aiming at more regular and predictive schedules with a reduction in night shifts in a row and with a reduction of shift types lead to lower biomarkers for IHD, and to a lesser extend to lowering robust stress biomarkers.

The change in shift schedule was validated with the use of RRPA. It showed that shift schedules in the intervention group at wards introducing all four principles changed non-significantly towards higher regularity and having only two types of shift (paired analysis). In the control group schedules changed towards less regular and predictable schedules, having also fewer Sundays off. Their schedules were also changed towards fewer hours worked a week. When comparing intervention and control groups, the intervention led to more regular and predictable scores, and to a higher degree of having two shift types. There were no statistically significant differences with regard to the number of

night shift in a row, or to circadian disruption. The changes in the group introducing 1-3 principles were smaller, and differences were not significant, neither in paired analyses nor when comparing with the control group, except for a tendency of a higher LW score and having more night work hours.

The perception of flexibility and predictability in the questionnaire changed according to the change in the intervention group.

The intervention group introducing four principles did not change sleep quality, there was a slightly better self reported health, but in general it did not lead to fewer symptoms of neither stress nor disease. The intervention group introducing 1-3 principles had lower stress symptom scores and higher scores on mental health after the intervention.

In the group introducing all four principles, both paired and age adjusted statistical significant comparisons with the control group showed lower values for glycated hemoglobin, LDL-cholesterol and total/HDL-cholesterol ratio, and higher values of HDL-cholesterol. In the second intervention group only fibrinogen was found statistically significant lower, but the changes were in the predicted direction for the rest of the lipids. The control group had raised total/HDL-cholesterol ratio and lower fibrinogen (paired analysis) during the intervention period.

Due to the problems of explaining the change in schedules in the control group, we also analysed differences between schedules one year apart, whether being a result of the intervention or not. Higher regularity were associated with a statistical significant fall in triglycerides and total/HDL-cholesterol. LDL-cholesterol was lowered with higher predictability. The reduction in number of consecutive night shifts in a row reduced total/HDL-cholesterol ratio.

There was a highly significant trend between

the number of ergonomic changes in a schedule and change in HDL, LDL, and total/HDL-ratio. Glycated hemoglobin also tended to be lower, all in parallel with the "intention to change" analyses conducted.

Publication V

Publication V shows that different shift work definitions (day versus non-day; night versus day, and non-night versus day) are related to biomarkers in different ways. The non-night versus day definition was associated to glycated hemoglobin and nonsignificantly with LDL-cholesterol, while the definition including night work was both associated with triglycerides and glycated hemoglobin. Especially the number of hours worked between 10 am and 6 pm in night shift workers was significantly related to lower HDL-cholesterol, higher triglycerides and higher total/HDL-cholesterol ratio, and to glycated hemoglobin. The broad definition of shift work was associated to higher levels of factor II-VII-X, mostly so with the non-night shift work.

Part time employment was associated with higher total cholesterol and LDL levels among shift workers. Regularity of the schedule were (non-significantly) associated to glycated hemoglobin, to higher prolactin, and to lower total- and LDL-cholesterol levels. For predictability, the associations were with total cholesterol and HDL, with triglycerides, and with a non-significant trend for fibrinogen and t-PAI, all, except for regularity and prolactin, in the predicted direction. For periodicity, there were significant differences in triglycerides, HDL- and total/HDL-cholesterol ratio, and a non-significant trend for fibrinogen. A high number of consecutive night shifts in a row were associated to lower HDL- and higher total/HDL cholesterol-ratio, and to trends for higher prolactin and

lower factor II-VII-X. This was no longer significant, when the number of night shift hours worked was entered into the models. The number of consecutive evening shifts were associated with a trend for higher

immunoglobulin A and a significant lower fibrinogen, somewhat lower when the number of evening shifts were entered into the model. The differences were not changed much when lifestyle factors were included.

Discussion

In the five studies presented together with this thesis it was shown, that:

- C The epidemiological literature suggests a relation between shift work and CVD (I), and that several pathways may be present to explain this relationship (I). However, these findings are not present in some methodological well conducted studies.

One methodological problem encountered in the literature is that confounding might be present, and it was shown that:

- C Social class differences are present between shift- and day workers (II and III), and
- C Work environment differs between shift and day workers in a random sample of the population, with the least favourable for the development of IHD belonging to the shift workers (III).

From these observations, the appropriate choice of comparison group will be discussed.

In another approach to explain the relationship between shift work and IHD, it was shown that:

- C Intervention in shift scheduling with the introduction of more ergonomically correct schedules with regularity and predictability as the main changes lowers biomarkers for IHD (IV), and
- C There seems to be different associations between shift work in- and excluding night work, the night work schedules mostly associated with the lipids, and with a linear relation between the number of night hours worked and biomarkers (V).

These results will be used to discuss both methodological problems relating to exposure assessment and information, and to discuss whether shift work can be regarded

as a causal risk factor for IHD.

Methodological problems

The heterogeneity of the epidemiological studies has not been explained. We have shown that at least two different groups of studies exists¹¹⁵, and that none of the study characteristics (publication year, area of study, exposure characteristics, outcome (MI, IHD, CVD), type of study, follow up period, confounding control) explain the heterogeneity. This is somewhat surprising, 1/3 of the literature is cross-sectional, and the selection processes discussed next will make it probable that the shift workers will be a survivor population. However, this was not seen in the meta-analysis. Another surprising finding was that the studies using aggregated exposure assessment had higher risk estimates than studies relying on individual assessment. Normally, aggregation would be biasing the estimate toward unity.

However, this analysis took only into account the information given in studies, and two major problems mostly unaccounted for in the literature emerge.

Selection bias and confounding

The traditional methodological problem described in relation to shift work research^{1,8,11,202,203} is secondary selection bias. A large proportion of shift workers leave shift work within few years, Harrington¹ suggested that 10% enjoy shift work, 70% accept it, and 20% leave shift work. In an older study in one company², 25% left shift work for day work within the first 10 years, 42% of these due to medical reasons. These figures for secondary selection are probably low, as people leaving for other factories or

trades would not have been counted. It also points at the assumption that the possibilities for finding other work will influence the rate. Some leave due to management changes, for instance when a company changes work schedule from three to two shift²⁰⁰, another group leaves due to changes in the social value given to the shift work, and a part due to health problems, for instance when experiencing gastrointestinal disorders. The latter explanation could both relate to the shift worker finding another job with day working hours, or to a referral within the company to a day time job, eventually by way of a company physician. The prevalence of workers selected out of shift work for the latter reason would be suspected to be higher when focus was on the relationship, and when factory doctors could dismiss people from shift- to day work. This means that the health based secondary selection will be larger when the physician know and trust that the selection is appropriate and possible. For IHD this knowledge would be at hand from the latter half of the 1980'th, after the study in Lancet⁷ and the review by Åkerstedt et al.⁸ first describing the risk. The fact that the selection process is relevant has been shown in literature finding a higher risk of CVD for ex-shift workers, a standardised mortality rate (SMR) of 160 (122-210 (analysed by us (I)) in Taylor and Pococks study⁴ and an incidence of 6/100 in shift workers after changing to day work compared to 2/100 in day and shift workers (no testing possible)¹¹⁹. In one study the difference between health based secondary selection and secondary selection due to managerial changes has been described. Thiis-Evensen found that ex-shift workers, that changed to day work due to health problems had higher absentism for CVD than ex-shift workers leaving shift work due to change of job²⁰⁴.

Explaining the health based secondary selection in relation to IHD indicates that some

kind of warning signals make the shift worker apply for a day job, or that some common feature is leading to both IHD and problems in adapting to shift work. One such possible common denominator could be stress (see page 16). The group continuing with shift work has been labeled a survivor population.

An anonymous referee for publication II suggested what could be labeled tertiary selection, meaning that people having IHD leaves shift work. The differentiation between secondary and tertiary selection in shift work is relevant in relation to the risk of ex-shift workers. If the shift worker has IHD when he or she leaves shift work, he or she 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. The distinction is not easy 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.

Less focus has been on the primary selection into shift work^{202,203}. People choose to apply for a shift work job with some kind of anticipation of whether it will suit them or not²⁰⁵. This judgement can be based upon former experience or solely on self judgement of for instance social possibilities or sleep habits. In a small study²⁰³ applicants for shift and day work were compared before commercing their new job. Neither had formal shift work experience, and besides being younger, the shift workers were more eveningness personality types with less rigid sleep patterns. This suggests that self-judgement is relevant. There were no differences in relation to social factors, symptoms or biomarkers (blood pressure, cholesterol, triglycerides) at baseline. This study was thus not supporting the idea that shift workers are a priory health-

hier than day workers, or that they are more stress resistant²⁰².

The literature has related the feeling of having chosen shift work to better adjustment to shift work¹⁷⁶, but it has not been shown whether the feeling of self selection influence biomarker levels or the risk of IHD.

In terms of primary selection the application for a shift working job can also be seen as the 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 the new applicants to a shift work job in order to obtain a day time job at a later time. In these situations the voluntary application could be a choice between shift work and no work at all. The situation at the labour market might thus influence both the primary and secondary selection processes.

Both in publication II, III and IV/V selection mechanisms may have been present. In CMS the population was middle-aged at entry (40-59 years of age), and they might thus have had 20-40 years of work experience before inclusion. The shift workers in danger of IHD could by this have left shift work. This is, however, not different from the majority of the longitudinal epidemiologic studies with individual exposure classification^{4,116,118} using cohorts with the same age structure, and of which two studies found a relation. From an ideal point of view, however, a cohort following the shift workers from their first entry should be preferred. In publication III, the population was a random cross sectional sample, and among the elderly with possibilities of selection. The same is true for the NARFE project, where most of the day working controls had previously had shift work.

In other words, it is not a random sample of people that ends up doing shift work. This

has potential impact on the first of the encountered methodological problems:

Choice of reference groups

The choice of the comparison group is crucial when the impact of shift work is assessed. Every comparison is done with reference to a nonexposed 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 being a day worker. The shift workers might differ from day workers socially, economically, and in personality factors. If the comparison group differs from the exposed groups in other relevant ways than the working time arrangement, eventually as the result of selection bias, potential confounding may be present. And as information on all possible confounders can't be obtained the differences will eventually not be controlled, leaving residual confounding.

In almost all of the literature encountered shift workers has been compared to day workers without questioning.

Social class

One of the differences between shift and day workers are the social class they belong to.

In publication III covering a random sample of employees we found that the distribution of shift work was highly screwed across social classes (table 4). In social class I more than 90% had day work, while this was only the case for 3/4 of social class V. Furthermore, the type of shift work differed, with night and three shift work being most prevalent in the lower social classes, while social class I was nearly only related to irregular working hours. In a random sample of the population shift work would thus be con-

	Social class						Total (n)
	I	II	III	IV	V	Under education	
Day time	91	80	81	84	74	87	4791
Irregular working hours	8.4	13	10	4.9	11	7.5	600
Evening or two shift	0.6	3.9	5.0	3.7	8.5	3.1	283
Night or three shift	0	3.0	3.4	4.2	5.8	2.0	212
Total (n)	716	1048	2049	569	1249	255	5886

Table 4. Working time arrangement by social class. Percent. Due to rounding columns do not sum to 100%

founded by social class as day work is more prevalent in higher social classes, and the type of shift work is screwed with shift work including night work being more prevalent in the lower social classes. Among females the differences were smaller (III)

The association between social class, shift work and IHD can be further analysed in publication II. The Copenhagen Male study is not a random sample of the population, but rather consisted of men in larger companies. The effect is that shift work is most prevalent in social class III with nearly 50% shift working. Figure 3 depicts the 22 year incidence of IHD. It shows that the incidence nearly doubles from social class I and II to social class V. Within each social class the incidence between shift- and day workers are nearly the same, a little lower for shift workers in social class I - III and a little higher in social

class V. It shows that social class will act as a strong confounder if not controlled.

Even if a single factory is studied day workers in the production will tend to be skilled workers, while shift workers will more often be unskilled. This would - in the Copenhagen Male Study - be a comparison between social class IV and V, the two right most groups and would lead to the social class differences in incidence still being larger than the differences between shift and day workers. In the Knutsson et al study of Swedish papermill workers⁷ this was in fact the comparison made. Shift workers at the papermill were unskilled production workers, and they were compared to day working skilled maintenance personnel. It means at the same time that controlling would be difficult if interaction was taking place, when there are only few skilled shift workers in this type of study.

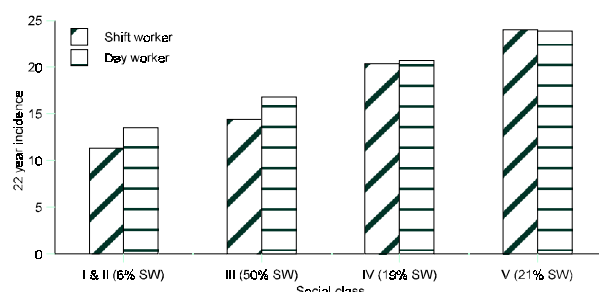


Figure 3. Incidence of IHD over 22 years in day and shift workers by social class

Of the remaining epidemiological studies (I) social class was controlled together with other potential confounders in the Kawachi¹¹⁶ study of female nurses (for spouse' education), in the McNamee¹²⁰ study (jobstatus), the Knutsson case-referent study¹¹⁷ (education), and in the Tenkanen study¹¹⁸ control for jobstatus was done by stratification in a way that enables a closer look at the effect. The relative risk for blue and white collar workers joined (age adjusted) was 1.52 (95% CI 1.11-2.07) and for blue collar alone, (age

adjusted), RR was 1.35 (0.94-1.93).

The figures do not give the possibility to examine the effect of shift work in white collar workers, and in general, the literature is focussing on the lower social classes.

The missing control for social class differences will bias risk estimates upwards.

Work environment differences

Another potential confounder is differences in work environment between day and shift workers.

In publication III all IHD risk factors analysed except quantitative demands, dust and long working hours were more prevalent in the shift than in the day working population. Furthermore, differences in the distribution of factors between irregular working hours, two shift/permanent evening and three shift/permanent night shift were present.

Even when controlling also for differences in social class between day and shift workers, differences were still present between the groups in some instances even with higher odds ratios than when unadjusted. Both observations are probably a result of sampling in different work situations (shift work being more prevalent in certain industrial and service sectors (especially the hospital)), and it would be expected that if a shift and day working group were doing the same tasks at the same work place, differences would be diminished.

Comparing day and shift workers without properly controlling for work environment factors would this way cover differences in other working environment factors, and shift work might be seen as a proxy measure for these other relevant risk factors. The results again suggests a bias upwards if not controlled.

As shift work types differed in relation to prevalences of work environment factors, and shift work type was also screwed among social classes, it would seem to be relevant to control for both factors.

The literature has in general not controlled for work environment differences. It has previously been shown that shift workers are more likely exposed to noise²⁰⁶ and passive smoking²⁰⁷. Only a few studies have controlled for differences in relation to IHD, and mostly so in relation to job strain^{118,208}, while Åkerstedt et al.²⁰⁹ controlled for (aggregated) information on several work environment factors.

Other risk factors

It has repeatedly been shown that day and shift workers differs in relation to personality factors, shift workers scoring higher on neurotism and hardiness scales, although the findings are not consistent¹⁶³. In the NARFE II project, constituting the base for publication IV and V, internal comparisons between shift workers with fixed and rotating shifts revealed differences in relation to Locus of Control and coping strategies²¹⁰. The literature does not contain studies that have examined the distribution between day and shift worker of personality factors relating to IHD, for instance hostility⁷³, and the personality factors shown to be related to shift work have not been shown to be risk factors for IHD (e.g. sleeping patterns, neurotism etc).

Confounding or mediator

On the other hand, not all differences should be controlled. One problem in the examined literature is the apperent confusion over mediating variables and confounders. In many of the reviewed articles (I) controlling have been made of every difference found

between the groups. The question has been posed: Is shift workers “born or made”¹¹ (p. 5), that is, were the differences present before starting on the job or are the differences a result of shift work experience. In the first instance, controlling of the differences should be made, in the second it may be more appropriate to see it as an effect of shift work.

A confounder is defined as a factor that meets all of the following three conditions: 1) It is a risk factor for the outcome of interest (i.e. heart disease), 2) it is associated with the exposure under study (shift work status) in the source population (the population at risk from which the cases are derived), and 3) it is not affected by the exposure or disease²¹¹ (p. 123-5). A mediating variable, on the other hand, is an intermediate step in the causal path between exposure and disease

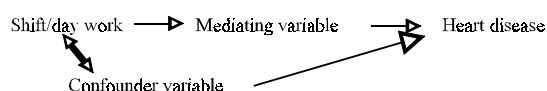


Figure 4. The difference between a confounder and a mediating variable

(figure 4).

As an example, some studies have controlled for differences in blood pressure between shift and day workers^{116,118,120}. Blood pressure is a risk factor for IHD and is associated with shift work status in some studies, but it might be affected by the exposure in this way being a potential link between shift work and IHD with blood pressure higher *because* of shift work¹³³, thus not fulfilling condition number three. When controlling by way of restriction to normotensives in the study design or by adjusting in multivariate regression analyses the effect will normally be a artificially lower risk than is really present,

except when confounders are nondifferentially misclassified. In that case bias can be in either direction.

In the study by Tenkanen et al.¹¹⁸, differences in lipids were also controlled but as higher cholesterol can likewise be regarded as an effect of being a shift worker (cholesterol related to the amount of night work (V)), lipids should also be regarded as a mediating variable.

Smoking and BMI have been controlled in all of the studies where it was measured^{5,7,116,118,120,207} and also in (II) but it is open for debate, whether differences in smoking and BMI acts as confounders or whether they are a consequence of shift work. For instance smoking may be regarded as a coping strategy of stress related to shift work, and higher BMI could be due to a changed metabolism at night. Likewise, whether exercise should be controlled can also be discussed.

In these circumstances, it would seem prudent in general to give both estimates uncontrolled and controlled for these factors, which was done in publication IV and V.

Of the discussed confounders related to IHD, the following can under no circumstances be regarded as potential mediators: age, gender, social class, and work environment differences, and they should always be controlled.

Exposure assessment

The other main problem in the shift work literature is relating to the definition of shift work, as already pointed out by Åkerstedt and Knutsson 13 years ago²⁰⁵. In their contemporary review⁸ shift work was defined as “work beyond the conventional daytime third of the 24-hour cycle” (p. 409), and they pointed at the permanency of work hours, completeness of 24-hour coverage and regu-

larity in alternations as possible explanation for consideration. Not much work has been done since then.

Most of the epidemiological studies have been on rotating shift work. Some even seems to have included fixed evening and night shift in the control group^{116,212,213}. From a theoretical point of view there is, however, no indication that permanent night shift should not be related to IHD, and the study by Tüchsen¹⁷⁷ also finds higher hospitalisation rates among bakers that at an aggregated basis have permanent night work. In another study¹²¹ permanent third shift was not associated with (acute) risk of IHD. The demonstration in publication V of a relation between night shift work, the number of night hours in night shift workers and biomarkers even suggests that permanent shift workers might be worse off than rotating.

On the other hand, the two-shift and permanent evening shift has neither been investigated in any details. Even so, it is encompassed in the commonly used ad hoc definitions in the literature. In the study by Tüchsen aggregated evening work was a risk factor. The group covered taxidriver, workers in hotels and restaurants, cooks and waiters, all of whom may be night working as well. In publication V the different associations between shift work with and without night work and biomarkers suggests that night shift work could be related to a higher risk of IHD. It still remains to be shown that permanent evening or two-shifts without night work is a risk factor for IHD, and secondary 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 stated previously, evening work is mostly related to social problems while night work is related to physiological desynchronization of circadian rhythms.

Detailed shift work exposure

In general the characterization of an exposure should encompass its nature, the amount and the time relationship²¹⁴. Translated to shift work a thorough shift work exposure should encompass at least the following modalities:

- C The type of shift work. Whether evening or night work is included, whether the schedule is rotating or permanent, and whether the schedule is covering the whole week (continuous) or only weekdays (discontinuous). Even among shift workers the spare time in weekends is valued higher 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 strainful than non-continuous work. As with the questions raised above on evening work and permanent night work this statement is not based on empirical ground.
- C The schedule. As presented previously, a clockwise rotation¹⁸, and the number of consecutive night shifts in a row are leading to lower biomarkers¹⁹⁹. One unrecognised problem is that *if* the ergonomic criterias are of importance in diminishing the strain of the shift schedule, *then* a schedule following the ergonomic criterias should lead to a lower risk of IHD than a schedule not made according to ergonomic criterias, even when the amount of e.g. night work is the same. This makes it important to incorporate some kind of formal description and comparisons of shift work schedules (see p. 19). Even more so, a schedule that changes in one dimension will often have changes in other modalities as well, and often probably in a negative direction. As an example, the change in schedule from counter-clockwise to clockwise¹⁸ leads to

a better circadian rhythm, but at the same time diminishes the amount of social desirable weekend hours. One possible solution would obviously be to give the actual schedule with the start and stop hours of the shifts, and preferable with an indication of weekends. This has in fact been done by several authors (see table 5, p. 54), although they have not discussed it.

- C The amount of shift work per month or year. If shift work is a risk factor then the “concentration” would probably be relevant. The figure should probably be counting the number of different shift types worked (number of evening shifts, night shifts, weekends). Also this modality has only modest empirical data, but publication V showing a relation between the number of night shift hours and HDL-cholesterol, total/HDL-cholesterol ratio, and triglycerides points out the relevance of at least the amount of night work in the schedule.^[11] This would also be helped by the inclusion of the worked schedule, as the reader would be able to make the figures out for him or herself.
- C The number of years in shift work. There is some support to a dose-response in the sense of years on shift work. The study on Swedish papermill workers⁷ showed an almost linear relation between years in shift work and relative risk up until the group with more than 21 years of exposure. Also the studies by Tenkanen¹¹⁸ and Kawachi¹¹⁶ report dose-response between year in shift work and an increasing risk of IHD, while the essentially negative

study by McNamee¹²⁰ did not detect any dose-response.

One would then have to 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 number of year worked on this particular schedule. The approach has indirectly been used in the Knutsson 1986 study, where people at the factory were allocated by the number of years as shift workers. It works when the shift schedule has been the same in all of the years, this way making the first three bullets above the same for the whole period. In fact two different schedules were used²¹⁵, one up until 1975 and then a slightly different schedule up till 1983 when the study was concluded (see table 5, p. 54). The “older” shift workers who also would have the longest exposure would have had higher chance of working in both, and as the old one was worse in an ergonomically context, they would in theory be more exposed (bullet two above).

In studies, where different populations are included as in the other two studies mentioned^{116,118} (and as also would be the case in population based studies) the first three bullets is not the same for all of the shift workers and this makes it problematic to compare “years of shift work” between the members of the cohorts. The “integrated lifetime exposure” would have to be able to take into account that shift schedules differ as stated in bullet two and three above.

In population based studies with questionnaire data the exposed groups classified as shift workers might be covering evening workers, night shift workers with only a couple of nights a month etc, up to permanent night shift work in continuous operations. In general this misclassification of exposure would tend to diminish any real association

[11] Also the study by van Amelsvoort et al., showing (see note 8) that having more than five night shifts a month was related to more ventricular extrasystoles points at the importance of night work (appended July 2000).

between shift work and outcome, and it suggest that population based studies would show lower estimates. This is apparently not the case¹¹⁵.

It seems that exposure should be delimited to above a certain level, in order to have enough contrasts between shift and day work. Another problem is that many studies have used only information on exposure at one point in time (prevalent) and the respondent might this way have very little exposure. Another problem with the “prevalent” shift exposure is that it would be possible that a threshold effect was present, meaning that a certain amount of shift work (e.g. hours of night work per month or years of shift work) should be present, before the risk of IHD was raised. It would not be reasonable to believe that few months of shift work in a lifetime would raise the risk. Other studies have demanded at least 10 years of shift work⁴ in order to be classified as shift worker. This would on the other hand open for the possibility that only a well-adapted and maybe thus less affected survivor population would be selected as exposed giving a lower risk of IHD.

It would be relevant to include more information on past shift work experience in the population studies, and better questionnaires should be developed.

One worry is whether the respondent understand what is meant by shift work. In a few studies some kind of validation of the information of shiftwork^{16,120} has been undertaken, but in most circumstances the exposure has been taken at face value. In an unpublished observation we studied the answers in the SHEEP-VIP[12] database where two questions were used to construct information on exposure¹¹⁷. One question

was whether the respondent had shift work (“skiftarbete”), and if so whether it was two-shift, three-shift with continuous running, scheduled work or other types. Another question asked whether the majority of working hours had been between 6 am-6 pm, between 6 pm-10 pm or between 10 pm and 6 am (or combinations). Inconsistencies were present, people stating that they did not have shift work at the same time also indicated a type of shift work, or indicated that their working hours was mostly including the 6 pm - 6 am period. In numbers (excluding those with a type of schedule not assessable), 115 of 4106 (2.8%) stating that they did not have shift work had inconsistent answers. As the same type of misclassification among day workers would not be possible, differential misclassification would be the result. This could be the effect of (at least Danish or Swedish) respondents that perceive the word “skiftarbete” as belonging only to industry.

Four studies used aggregated exposure assessment^{5,6,177,209}. Instead of applying the exposure on every participant in the study, information on the prevalence of shift work in different occupations from smaller samples are utilised to give every participant in a specific occupational group the same exposure information. So if for instance employment as a bus driver is known for 75% of bus drivers to include rooster work then every bus driver in the population is viewed as exposed to shift work, including the 25%, that did not have shift work. Due to the misclassification this type of study would normally lead to lower risk estimates. This is not so in general, the studies seem to give higher risk estimates than studies using individual exposure assessment (I)¹¹⁵. This is even more surprising as the actual cut off point in two of the studies^{177,209} was as low as 20% exposure, with a potential misclassification of up to 80% of an occupation.

[12] Stockholm Heart Epidemiology Programme and Västernorrland Infarction Project

But even in the population based studies with an individual exposure classification the actual schedules are not reported. So for instance in the American Nurses study¹¹⁶ where shift work was defined as having worked for more than 1 year with more than three nights a month (and excluding permanent nights), this covers schedules with a wide variety of shifts. Having publication V in mind, the actual exposure might be very diluted.

The problem of misclassification of exposure is also related to the past exposure of the shift workers. In the McNamee study¹²⁰ a large part of the shift workers had been day working at some time before inclusion as shift worker. The median exposure of shift work was 10.7 years among the shift working group that had median 15.5 years of employment at the factory. So it would be relevant to count the total actual exposure.

Another problem in exposure assessment relates to the comparison group. Traditionally they have been day workers, but some studies included permanent night (see above) and one study included two shift workers³ in the “non exposed” group. Furthermore, in many studies the day workers could in fact have been having shift work before the day work (ex-shift worker), especially if only prevalent information is used. This is in particular the case for population based studies, and would dilute an effect as controls are misclassified as non exposed[13]. The severity of the problem is relating to a hitherto unaccounted characteristics of the relationship between shift work and IHD; If shift work is a risk factor, would exposed

people then have the same risk after the end of exposure or would the risk change? (as it is the case of cigarette smoking where the higher risk for IHD disappears within two-three years after cessation⁷⁶), so that it diminishes for instance over a couple of years after the cessation of shift exposure. In the case of a diminishing risk with time the problem of misclassification of exposure in non exposed would be largest when shift workers had just left, and be a less problem if ex-shift work was several years back. In an unpublished examination from the SHEEP-VIP case-control study we actually found that the risk of IHD related to shift work diminished within 3-5 years after shift work was left.

The information on exposure assessment in the studies from publication I is collected in tabel 5 at the end of the chapter. Several studies do not even give a definition of what is meant by shift work. Of the rest, approximately ½ give some details of the shift schedule in some instances with the possibilities to calculate the amount of for instance night shifts. Within these, most studies are three shift, rotating, and most of these with few night shifts in a row (see also p. 43).

In the Copenhagen Male Study (II) information on shift work were collected through self reported questionnaires at two occasions, in 1971-72 and in 1985-86. The information included one question, asking whether the participant had irregular hours, fixed evening or night work, or whether they worked day time only. The information was confirmed during a later interview. This means that the exposure was “prevalent” and it did not include neither type of schedule, amount of shift work, schedule characteristics nor life time exposure. Through the second baseline using the same questionnaire 14 years later some indication of the stability of exposure was obtained,

[13] Furthermore, ex-shift workers have been shown to have a higher risk than both day and shift workers. This could lead to substantial bias toward lower estimates, if the secondary selection was large (appended july 2000)

suggesting that those stating to have shift work at both occasions would be exposed. For social class III with approximately 50% shift workers we compared the self reported occupations from day and shift workers, and found that shift work was inherent as a natural part of the reported occupations for nearly 90% of the shift workers while the same occupational groups had only indicated day work for 4% of the sample, thus partly validating the information. But despite of this, we had no detailed information on exposure and especially not on the “concentration” or “dose” of the exposure.

The same is true for the NWECS (III). Shift work was defined as having answered yes to one of the possible answers: two shift, three shift with running shifts, three shifts with changing shifts, irregular placement in day or week after schedule, fixed evening, fixed night, early morning, others. This was then combined into night work including fixed night and three-shift work, evening including fixed evening and two-shift work and other irregular working hours. This way the information is prevalent and covers a wide variety of work schedules. Two-shift work can also be covering two times 12-hour shift.

In population V we examined different types of shift definition on the association with biomarkers. Differences occurred between shift work including and excluding night work, the latter associated to biomarkers for IHD while the exposure to evening shift work was associated to glycated hemoglobin, a stress marker, but only marginally to lipids. This suggests that the night component of shift work might have potential impact on the magnitude of the risk.

Measuring ergonomic criterias

As stated above the ergonomic criterias should be accounted for in the shift work exposure assessment in order to be able to take into account that different shift work schedules might confer different risks.

In publication IV and V the problem of exposure classification was elaborated. As a consequence of the very individual schedules used at the hospital wards a way to compare both the new and old schedule for the individual and to compare schedules between subjects was needed. A further problem was the fact that the ergonomic principles encom-

pass very different features of a schedule, and it is problematic to compare for instance a schedule with only three consecutive nights in a row but a backward rotation with a foreward rotating schedule with four nights. The RRPA was used for this purpose. The program evaluates criteria that are not entirely the same as the 14 criterias from the BEST-group (see p. 19). Although the number of shifts in a row is included in the periodicity-score, and the overall number of night shifts mirrors in the opportunity to rest at night (ON)-score, we further counted the maximal number of night shifts in a row and the number of night shifts in the schedule. The same was done with evening shifts.

Among the changes made, the reduction of number of different shifts is not identified directly in the RRPA, and we also counted the number of different shifts in the schedule.

	m	t	w	t	f	s	s	m	t	w	t	f	s	s	m	t	w	t	f	s	s	m	t	w	t	f	s	s
D	d	d	d	d	d			d	d	d	d	d			d	d	d	d	d			d	d	d	d	d		
N	n	n	n	n	n	n	n								n	n	n	n	n	n	n							
M	n	n						n	n			n	n	n	n	n							n	n			n	n
a	a	a		d	d			d	d	d		x	n	n								n	n	n	n		d	d
	d				d	a			n	n	n				d	d	d	a	a			d	d	d		n	n	
b	y	n	n	n				d	d		d	d	d	d				d	d	d		d	d	d		n		n
	n			d	d				d	d		n	n	n	n			d	d			d	d		d	d	d	d

Table 6. Five schedules with different characteristics (see text). d=day, a=afternoon, n=night, x=day shift followed by night shift, y=short day shift (until noon) followed by night shift

score	day shift (D)	7+7 night shift (N)	5+2 night shift (M)	rotating shift: pre intervention (a)	rotating shift: post intervention (b)
RE	10.0	10.0	10.0	7.9	7.2
PE	10.0	1.4	3.7	6.6	6.9
LS	8.3	8.0	8.0	7.9	8.2
LW	8.3	8.5	8.8	8.6	8.5
ON	10.0	4.9	5.1	7.8	8.2
PR	8.3	7.5	8.3	4.2	5.1
OH	4.5	10.0	10.0	7.4	7.0
OE	10.0	10.0	10.0	8.7	10.0
OW	10.0	5.5	5.5	5.5	4.7

Table 7: RRPA scores for the schedules shown in table 6

For comparison and in order to establish a couple of waypoints the RRPA scores for shift schedules from the wards are presented (table 6 and 7). The first schedule is for comparison, a discontinuous day shift (normal day shift, Monday-Friday 8.00-15.24, marked D in the table), followed by a permanent 7/7 night shift schedule with 7 consecutive night shifts and 7 days off (28 hours a week, 196 night hours 22-06 in 8 weeks, marked N). The ergonomic better 5/2 night shift with the same number of hours is also presented, marked M.

Most of the schedules in the NARFE project were irregular, one of these schedules selected at random from the intervention ward B where the largest change was found, is presented ((a): pre intervention, March and April 1997, and (b): post intervention, March and April 1998).

The schedules ran for four weeks, but eight weeks was used in calculations to diminish the impact of holiday and vacations (and one ward went from 4 to 12 weeks of schedu-

ling). For comparison (the constancy score and the PR (predictability score) depends on the number of weeks) the first three shifts schedules are also defined as 8 week schedules (although they would normally be running in a 4 week schedule, and in reality are 1 and 2 week schedules repeating themselves).

It can be seen from the RRPA-figures (table 7) that the day-only shift is better than all of the other shifts presented, that the 7+7 night especially lowers the physical figures (PE and ON), and raises OH, that measures the amount of time off in weekdays. The proposed change of the permanent night shift with a split of the nights in 5+2 consecutive nights gives the predicted change with better values in the physical (PE, LW and ON (due to the accumulation of fatigue)), but also a slightly better PR-score, which is brought about by a change in the constancy score rather than the basic score. This is due to the 5/2 system giving days off every week which the program evaluates as an advantage in agreement with the literature¹⁸⁰.

The rotating shift (a) is less regular (RE) and predictable (PR) than both the permanent day and night shift. The ON and PE scores are in between the day and night shift, as the number of night shifts is lower.

The change (b) brings lower scores of regularity but higher on predictability and a higher ON and PE score due to having more night shifts in 8 weeks. The change in predictability is probably due to the change from 3 to 2 shift types. The OW falls due to fewer Sundays off (5 in a, 4 in b), and the OE is 10 because there is no evening shifts in (b).

The RRPA scores from the intervention example shows the problem in comparing scores: The changes that included a reduction in the number of types of shifts from three to two at the same time gave more night shifts in the eight week period, which affects the PE and ON score negatively. So a positive change in one score is followed by a negative change in another.

The different criterias are not independent and a factor analysis with varimax rotation of the schedules at baseline in publication V showed that the combined RRPA-scores and the extra figures taken from the schedule loads on four different partly independent factors measuring:

- nights (PE-, ON-, OE-score, maximum and total number of night shifts, maximum and total number of evening shifts),
- number of non-day time hours (OH-, OW-scores, number of shifts, number of sundays),
- a regularity score (RE-, LS-score, PR-score, number of shifts) and
- a working week length score (LW, number of offences against the 11 hour rule and number of times with less than 36 hours between blocks of shifts).

As the scores were highly correlated, especially PR and RE, it was necessary to choose among the scores.

The RRPA was used in two manners. In publication IV it was used to validate whether changes were in fact made at the wards agreeing upon this. It showed that regularity rose in the intervention group introducing four principles, but that periodicity as a measure of circadian disruption did not change. This is in accordance with the fact that the number of night shifts in a row was not changed either.

The RRPA was also used to measure changes in scores by dividing the change into better score, no change or worse score regardless of whether the change was a result of the intervention or not.

In publication V we used RRPA to characterize the shift schedule in order to measure for instance the regularity or periodicity of shifts. In this context one problem is that it is hard to translate a RRPA figure into a meaningful construct and that the scores are not necessarily measures on a ratio-interval scale, so we chose to use them as rank scales and used the scores divided into tertiles in a linear regression model.

In order to demonstrate the possible positive effects on shift work exposure assessment using the RRPA-approach, I have used the RRPA on the publications on shift work, biomarker measurements, and IHD in which the authors gave information on the actual shift schedule, that is the sequence of shifts, the placement of weekends (or if a schedule was completely described by the sequence and an indication of the schedule length), and the start and stop hours of the shifts. This information is placed in table 5 (at the end of the chapter (p. 54)), while the RRPA-figures is found in table 9, also at the end of the chapter.

This approach to evaluate exposure assessment in the literature reveals two features. In the intervention studies where two schedules are being compared, there are changes in more than one RRPA score and often in opposite directions. In the clockwise-counter-clockwise rotation experiment¹⁸ the better periodicity is accompanied by much lower opportunity for weekend recreation (as was also the reason for the police officers to prefer the counter-clockwise rotation). In the study dividing the night shifts in a row¹⁹⁹ the negative effect of better periodicity and predictability is a lower score on regularity.

Secondly the schedules have very large differences in their RRPA scoring, with for instance regularity ranging from 6 to 8.5 suggesting that the shift exposure in the literature is very different. Again, if ergonomic criterias are related to the risk of shift work this would be possible explanations for the different results. If for instance regularity is related to biomarkers (as suggested by publication IV and V) then when using very different schedules the exposure might be very different and it would argue that studies should give more information on the schedules.

For instance Angersbach¹¹⁹ and Knutsson²⁰⁸ used shift workers from several different schedules. They internally differed with regard to RRPA scores and in relation to publication V might have very different exposures. It would have been interesting to know whether the inclusion of schedule characteristics led to differences in risk.

Compared to the baseline RRPA scores in the NARFE intervention (IV, V) the literature has ranges on both regularity, predictability and periodicity, that covers the median baseline figures and are thus comparable. The load in week figure is higher than in the literature which mirrors that part time employment was a feature of the hospital

wards. The “opportunity for rest at night” and “evening recreation” figures were also higher in the NARFE project suggesting that the number of night shifts was lower than in industry, and thus in the majority of the literature. Finally, most literature studies had lower figures on “opportunities for weekend recreation”. One characteristic of the schedules in Danish hospitals are that weekends have high priority and most often with both saturday and sunday off which is possible because staffing are lower at weekends. This will on the other hand tend to give more irregular schedules.

To summarize, a valid exposure measurement should include information on type of shift work, schedule characteristics (through the inclusion of the schedule in the material section of the paper or for instance with the RRPA scores), “concentration” of relevant features, and the “dose” in terms of for instance years. Whether it would be possible to concentrate all of this information in one figure is doubtful but will rely on future information on the relative importance of different features of the schedule.

One possible place to start would be to include hours worked at night in a reference period. In relation to the discussion on the reference group an alternative would be to select different shift schedule populations with homogeneous RRPA measures and compare them for the importance of different components. This would also mean that smaller differences in relation to possible confounding between shift work and reference group would be expected.

Measurement of biomarkers

Another problem relating to information is circadian rhythmicity of biomarkers. It has been shown that also lipids have a circadian rhythmicity (see p. 15). It is well known that

the circadian change due to night work is always a change in acrophase and a somewhat lower amplitude¹²⁹. This means that a measured difference between day and shift workers or in different shifts could be the result of measuring at different places on the rhythm (figure 2).

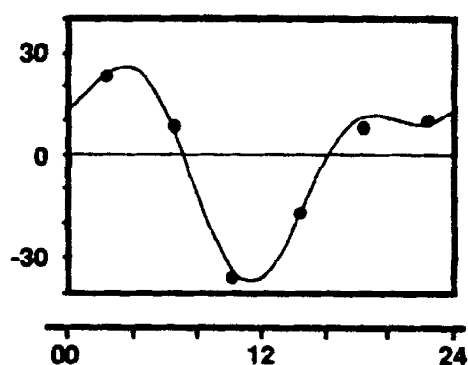


Figure 5. Circadian rhythm for triglycerides. Per cent deviation from arithmetic mean. From Rivera-Coll et al., 1994

Whether the acrophase would be advanced or delayed in the night worker is a matter of the timing of sleep, but in a circadian rhythm with the highest value early in the night and a steep decline in concentration during the morning hours (as triglyceride)¹⁴⁰ the result of a phase delay of just 4 hours would lead to the measurement of maybe 25% higher values at 8 am (see figure 5).

Table 8. Sampling of blood in studies on shift work and biomarkers

First author, year	Blood sampling characteristics given in the publication
Bursey 1990 ²¹⁶	During mornings, for shift and day workers alike
Bøggild 1999 (II)	In the morning, after fasting

Cesana 1990 ²¹⁷	?
Cesana 1985 ¹⁵⁷	In the morning
Costa 1990 ²¹⁸	Morning after a night off-duty
De Backer 1987 ²¹⁹	In morning shift
Kecklund 1994 ¹⁹⁹	In the morning, after fasting
Knutsson 1989 ²²⁰	Morning after a nights sleep, fasting
Knutsson 1988 ²⁰⁸	Morning after a nights sleep, fasting
Knutsson 1990 ¹⁴⁷	Morning after a nights sleep, fasting
Lasfargues 1996 ²²¹	After fasting overnight. In discussion night shift workers may not be fasting - > after nightshift?
Lennernas 1994 ¹⁴⁶	In a day shift (~ from schedule it means > 72 hour)
Nakamura 1997 ⁸⁶	On morning shift, after one night fasting
Netterstrøm 1996 ²²²	?
Orth-Gomér 1983 ¹⁸	After a nights sleep
Peternel 1990 ²²³	Last day on morning shift, last day on night shift
Romon 1992 ²²⁴	Between 7 and 8, morning shift for shift workers, 12 hour fasting
Thelle 1976 ²²⁵	?
Theorell 1976 ²²⁶	Day time, 1. and 3 week (from figure)

The other lipids have the lowest values in the morning, and a much lower variation, so they would probably be less affected.

The literature in general does not provide detailed information on the timing of blood sampling in relation to working hours, i

nformation in studies from publication I is gathered in table 8.

It seems as if most studies demanded one night off which means the possibility of having only 24 hour between the end of the last night shift and blood sampling.

Lennernäs¹⁴⁶ had at least 72 hours between the last of five night shifts and blood sampling. On the other hand, Lasfargues²²¹ while claiming a overnight fast in the discussion indicates that the night shift workers might have been eating (and thus awake) and his finding of a higher triglyceride level of shift workers could in theory be a result of this. In a recent study¹⁶¹ sampling was done in the morning, after either day work, a day off or night shift, thus also having the possibility of measuring the desynchronized circadian rhythm.

In normal persons the biological half-life of LDL-cholesterol is 3-5 days and for HDL-cholesterol 5-7 days⁷⁴. Fibrinogen has a biological half-life of 3-4 days²²⁷. It has therefore been suggested⁷⁴ that the acute changes (within hours) in relation to acute stressors are probably reflecting changes in plasma volume that is also subject to circadian rhythmicity¹³¹ more than the amount of lipoprotein.

In publication IV and V we used an approach of having at least three days after a night shift before measuring. Although it is not known how long the circadian rhythms of lipids need to return to day orientation, most measured rhythms have a quick return¹²⁷. The alternative approach would be to measure several times at the same day in order to establish the circadian rhythm before finding the relevant value. This would also allow for studying the acute effect of shift work on lipids.

Some¹³³⁻¹³⁶ but not all¹³⁷⁻¹³⁹ studies with 24 hour measurements of blood pressure have suggested that there are differences in blood

pressure between day and night shifts, one study suggesting a longer high plateau of systolic blood pressure when working in the night compared to day work (20 hours versus 14) although the mean pressure did not change¹³³. By analogy, this could in theory mean that the lipid influx into the vessel wall was longer lasting and could change the equilibrium of atherosclerosis⁷⁶.

Different biomarkers may have different rates at which they respond, remain elevated and return to normal²²⁸. This has not received much attention but it would not be surprising if metabolism in some instances were capable of down regulating the response, so for instance a stress biomarker was lowered⁷⁵. This might especially be a problem in the fibrinolytic/hemostatic system with its numerous feed-back systems⁸³ and could be an explanation on the essential negative results in publication IV and V.

For the stress biomarkers we chose glycated hemoglobin, immunoglobulin A and prolactin. For IgA most measures have been done in saliva and it might have been more reasonable to use IgG²²⁹ or IgM as markers of the system, although the use of these as biomarkers of stress have had less attention in the literature¹¹⁰. In theory especially IgM would be more robust than IgA. The use of prolactin as a marker was troubled by very large variations and it did not behave as expected. We did not include the traditional stress biomarkers (epinephrine, cortisol). This was chosen as the use of these is in general not well suited for field studies due to the variability, requiring several measurements¹⁰³, and it will as a measure too close to the beginning of the cascade give the possibility of a feedback tending to maintain values within a narrow physiological range¹⁰⁴.

In relation to IHD the use of lipids and lipoproteins as biomarkers are well validated⁵¹. The choice of factor II-VII-X and t-PAI as

markers of the hemostatic system are debatable, but were chosen on the basis of both being shown to be risk factors for disease and to the actual possibilities at the local Department of Biochemistry (besides PAI all analyses were part of the routine possibilities). This was done in order to obtain the most unproblematic analyses as laboratory variations should be the smallest possible.

The biomarkers are used as surrogate end points for actual disease and this pose at least two problems. The use is only valid if the biomarkers are actually causally related to the endpoint²³⁰ (IHD and stress). The other point is related to the discussion above; if some feed back in the system maintain equilibrium the use of biomarkers are not a valid surrogate of the diseases, unless the risk of disease also change when the biomarker is held at normal concentrations. On the other hand, the alternative would be large scale trials running for years and with numerous problems in relation to statistical power and distant outcomes²³⁰ besides the problems relating to selection and changes in exposure over the years.

Information from questionnaires

Most information in both the CMS, NWECS and NARFE II projects was obtained from questionnaires. This poses potential problems especially when trying to measure constructs as disease, stress, sleep quality, and social conflicts. The building of scales can easily be misleading²³¹ and scales should be subjected to psychometric validation. We chose most of the scales for the questionnaires in NARFE II from literature governed by theoretical considerations. As we conducted an intervention, the scales were chosen so that the floor and ceiling properties made it likely that changes would be possible to detect (thus for instance leaving out most of the

Short Form-36). Most of the scales came from the Standard Shiftwork Index²⁰¹ which is a set of questionnaires selected for shift work research, but as especially the stress outcomes are not part of the SSI others were selected for specific purposes. Where possible we obtained the Danish versions, but for the SSI and others we translated them from English to Danish and back and discussed the translations. In some instances we were not able to find existing scales (for instance on adaptation to shift work) and in these instances we made up our own scales. This was done by first selecting the field for which the scale should cover, then we were independently setting up questions and discussing the proposals, before agreeing on the selection of questions for a scale. The resulting questionnaire was tested in a small pilot study in a telephone company.

The scales were subjected to psychometric testing in the first questionnaire (just before the intervention). For all scales the Cronbach alpha, item-scale correlations, and factor analyses were conducted. For scales taken from the literature the factor analysis was used to test whether we found the same constructs as was given with the scale, for our own scales it was used to describe the internal properties of the scale. For most of the scales from the literature there were acceptable properties with Cronbach alpha ranging from 0.5 to 0.9 and in most instances with acceptable item-scale correlations. A scale on dietary habits was not working as a scale. For our own scales a couple had very low Cronbach alpha's and were obviously not working as scales.

But although the internal properties of the scales were in most instances reliable and valid, the external validity of the scales were not tested as this would demand a golden standard. For both symptom scores and stress this might be a problem.

For stress the measurement is of subjective feelings, a “snapshot”²³² of a transaction between environment and the individual. As stress in the Lazarus’ mode include an appraisal of threat, challenge or harm, it seems hard to obtain valid information through a questionnaire. Instead we used Setterlinds stress symptom questionnaires²³³ which would be a measure of the *results* of a stress process. In general no changes were found on symptom scores in relation to the intervention, and one might wonder whether this result really is valid; The changes were regarded as positive from the large majority of participants, and it might be possible that they would be experiencing less stress. It could simply be that the questionnaire was not capable of detecting smaller changes in stress perception not leading to lower resulting symptoms.

Dietary questions were included in the diary, but the response rate was low. We instead used a single question from the questionnaire as a marker of the use of fat, but this only gave information on baseline dietary habits and was not related to changes in biomarkers. The literature suggested that the distribution of carbohydrates over the night shift is related to cholesterol¹⁴⁶.

Intervention and biomarkers

The intervention in publication IV led to changes in biomarkers. We were able to control for some but not all lifestyle factors. The information used to adjust were from baseline data, and it might be postulated that the effect of the intervention was working through changes in these factors. Former studies¹⁴⁷ have not found lifestyle habits to change at such speed[14] and in our study

the use of tobacco, alcohol and exercise did not change during the period either (IV).

Goldenhar and Schulte¹⁸⁶ reviewed intervention research in occupational health and safety between 1988-93, and among 36 studies they concluded that the magnitude of studies lacked theory, were small and did not have the intensity in intervention to suspect a change to occur. In our intervention study we had a theoretical background governing the suggested changes in shift scheduling.

The changes were seen in the biomarkers with the smallest variance, and the reason for not finding changes in some of the stress biomarkers or in the markers for hemostasis might be that the study was too small.

Whether the intervention was large enough, is not easily answered. It is clear from the attempts to validate the changes obtained, that no change was seen in the periodicity score and in the number of consecutive night shifts. It turned out when the schedules were collected just prior to the intervention, that many already had 3-4 night shifts in a row at both the intervention and intervention control wards and some also had two shift work. There were changes in the regularity score and in the number of participants with a change from three to two types of shifts, but the changes were small.

It is a paradox that the control group had the largest negative change in schedule characteristics (in the paired analyses). It could be a result of the changes putting restraints on the possibilities for scheduling also for the controls at the intervention wards, but the change was seen in both the internal (at the intervention wards) and in the external controls (at the intervention control wards). Another more possible explanation was that the frames for scheduling were changed

[14] Although van Amelsvoort (see note 7) found smoking shift workers to smoke more over a year

(appended july 2000)

through new agreements on overtime work. Eventually some of the statistical differences are the result of a larger control group.

We chose to analyse the data in a modified “intention to treat” way dividing participants in groups after their potential change, knowing that some of them did not have their schedules changed. This was the result of the main interest of the study, to examine whether the introduction of principles could lead to changes. The reason for this was that the wards had planned to schedule after the principles, but were not necessarily able to do so (especially on two of the wards) due to staff shortage et cetera. This approach will inevitably lead to lower power of the study.

Evidence of a relationship

In determining whether shift work raises the risk of IHD there must be a plausible causal connection between the exposure and the risk. In publication I the model described prior by Knutsson¹⁶ was elaborated to incorporate changes in biochemical risk factors (biomarkers) (see figure 1) and the literature was reviewed in line with the model. The general conclusion of the review was that previous research has focused on life style changes and changes in markers of atherosclerosis, while other possible pathways being mismatch of circadian rhythms and disturbed sociotemporal patterns have only indirectly been described.

The results in the literature were not consistent. In six of 15 studies shift workers smoked more, in one study less than day workers. In two of 10 studies shift workers drank more alcohol while one found a lower prevalence. In one of five study shift workers were exercising more and in one less. Weight or BMI were higher in two of eight studies. Diet has been studied in six studies and in general there have been found no differences

with regard to intake of lipids while shift workers seemed to snack more, mostly so with higher carbohydrate intake. These lifestyle changes seems to be pointing toward smoking and dietary habits as important in explaining the relationship between shift work and IHD. It 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 they do not in others.

The relatively large amount of literature on lifestyle does not mean that the other possible pathways could not be potentially as important. With regard to the mismatch of circadian rhythmicity MI and AP have been shown to have higher incidence in the morning and a peak in the evening²³⁴ has been related to awakening after day sleep. In the causal chain the metabolic relationship between patterns of nutrition and the circadian rhythmicity of biomarkers could be of importance. The sleep changes related to shift working have been investigated³³ and sleep apnoe syndrome has been related to IHD^{235,236} but it has not been shown whether sleep quality or sleep length are related to IHD, and whether sleep apnoe are more prevalent among shift workers. There are gaps in the knowledge at these points.

The finding in publication IV that an intervention in shift scheduling aiming at less strainfull shift work leads to lower biomarkers with the changes being highest in the group changing the most, and in publication V that among a relatively homogenous group of night working nurses and nurses aides the number of hours worked between 10 pm and 6 am were correlated to concentrations of HDL-cholesterol and triglycerides suggests that the causal effect is real. It is in line with the study on clockwise and counter-clockwise rotation¹⁸ and on

dividing the night shifts in 3+4¹⁹⁹ both leading to changes in risk factors for IHD, and with a study from Japan²⁰⁰ showing that the abandoning of night shift in a car factory led to higher HDL and lower triglycerides.

What was linking the changes are not clear. It could be a result of shift work leading to circadian disruption, to stress, or to dietary habits.

Shift work and stress

In the literature stress has been described in shift workers as an important pathway to IHD, and it has been suggested that newer models of shift work interference with health has borrowed from the general literature on stress theory¹²³.

We did measure stress biomarkers and stress symptoms (publication IV). Stress symptom scores only changed in the intervention group introducing 1-3 principles. In general stress biomarkers did not change, except for a small but significant decrease in glycated hemoglobin in relation to the intervention (IV). Glycated hemoglobin was also higher among shift workers at baseline and associated to the hours worked at night among night shift workers (V). Prolactin behaved opposite of what was initially predicted. It has been shown to be higher when participants are passive¹¹². The interpretation of this is that the intervention group should be more passive through the six month follow up. This would mean that they were more active just before the intervention was made, and at time 1 their values were in fact significantly lower than the controls.

The approaches to measure stress in shift workers have not been theoretically well founded. On one hand, shift work has been labeled as a stress inducing factor (see p. 16) related to sleep disturbances and social life

conflicts, and on the other several studies have recently been published looking at stress in shift workers with the argument that shift work is leading to IHD and that stress might be one possible explanation. But the models used seems not to be appropriate. The Karasek-Theorell model measures skill discretion and decision authority which are organizational merits of the jobs. The questions include learning and development of skills, and conflicting demands and fast work to measure the amount of strain⁹³. None of the questions address the working time dimensions and although publication III suggests that shift work is associated with Karasek-Theorell types of job strain, it might be that the jobs are just more strained - not that shift workers are worse off than day workers if working in strained job. In publication IV we also included questions of the Karasek-Theorell model. In this context (all nurses and nurses aides) there were no differences between day and shift workers which was as anticipated.

The Effort-Reward-Imbalance approach views the imbalance in certain people of the efforts related to work itself with the perceived reward received. In this combination the ERI could be used to measure stress in shift work, regarding the extra efforts connected to the working hours as an extra strain and the rewards as for instance extra payment for odd working hours, time off at other hours et cetera as possible rewards for shift work. The existing questionnaire is however not relating to these aspects of work and as such ERI is not measuring working time related stress properly.

The importance of creating a theoretical approach covering shift work stressors - and ways of measuring it - is large. As stress is seen as a major contributor to shift work related disease, part of the explanation on the apparent heterogenic results could be that

some people perceive their shift work as stressful while others do not. This would lead to a better understanding of the effects and to potentials for prevention.

Is shift work a risk factor for IHD?

The ultimate question is whether shift work is a risk factor for IHD. The immediate answer is that the literature suggests an association with a relative risk of 1.4 being the most reasonable guess of the strength. But then, the discussion points at several methodological problems and the question is maybe more problematic than at first glance. In line of the previous discussion it could be rephrased to:

Is it a causal risk factor?

It might be that confounding makes shift work a proxy for other risk factors some of which have been controlled for in the literature, but both differences in social class and work environment might theoretically be responsible for the results (publication II and III).

Among several proposals for criteria suggested to indicate a causal relation (as opposed to a statistical association), Hill (expanding a report from the Surgeon General Advisory Committee on smoking and health) suggested nine aspects to be relevant to judge between the two situations²³⁷. Rothman and Greenland have warned on using them as checklists, giving examples of situations where the arguments does not hold²³⁸. With Rothman and Greenlands warnings in mind the case of shift work and IHD is put up against the Hill criteria:

Strength of the association: The literature review (I) suggested - in line with previous reviews - a risk of 1.4 to be the most plau-

sible. In the metaanalysis¹¹⁵ arguing that the aggregated studies were from another "population" of studies we identified two groups of studies, the "positive" with a homogeneous meta-estimate of 1.31 (1.17-1.45). The previous discussion on shift work as an exposure would however questions whether these four studies are examining the same relationship and the result must therefore be carefully interpreted. Even so, this is not a very strong relationship but although a strong association is normally regarded as a sign of causal relationship, Rothman and Greenland cites several examples of exceptions from this rule going in both directions. Nevertheless, a weak association gives the possibility of an unaccounted modest confounder to be responsible for the association.

Consistency: The studies (I) were very heterogeneous, some finding no associations others up to a risk of roughly 2. The metaanalysis showed two subgroups of studies, one essentially positive, one negative. This could suggest that shift work in some instances were related to IHD while in others there were no risk attributable to shift work. I comment more on this in the next section.

Specificity: The original idea of Hill was that a cause could only lead to a single effect. Shift work is besides IHD related to sleep problems, gastrointestinal disease and social disruption. Rothman and Greenland gives several examples showing that this aspect is entirely invalid.

Temporality: That the exposure is present before the effect is a sine qua non in judging a causal inference. This means that shift work should lead to IHD in workers that were free from disease at the entry. This has been the case in most of the cohort studies.

Biologic gradient: Knutsson⁷ demonstrated a dose-response up until 20 years of shift work. Two other studies found more modest

dose-response curves, but as discussed under the exposure section (p. 38) a possible explanation could be a misclassification and dilution of exposure. Rothman and Greenland shows that a dose-response is not necessarily a sign of a causal effect, a confounder, that is higher for the most exposed could likewise produce this result. Social class should not be able to produce this result, but if harmful working conditions were more prevalent among shift workers (had a higher OR) back in time and had been approaching the prevalence in day workers with time, this could theoretically give rise to the dose-response curve described. Publication III is cross-sectional so the results of the age stratification are not able to show whether this is true; it is however not entirely unrealistic that it could be the case.

Plausability and coherence: Originally they were seen as two different aspects, but as the distinction between them is hard they are evaluated as one. The model and discussion on a causal web in publication I suggest that shift work could be plaining through known risk factors. However, it should be remembered that it is entirely based on beliefs²³⁹ it might both be that the model is entirely wrong, or that the suggested findings are not related to shift work. The demonstration of an effect of intervention on biomarkers in publication IV and of a relation between number of hours worked at night among night shift workers and biomarkers in publication V gives plausability to the claim.

Experimental evidence: There are no direct animal experiments on shift work and IHD. An experiment with hamsters that were genetically susceptible for the development of cardiomyopathia showed that a weekly reversal of the light-dark cycle of the hamsters led to shorter lifespans²⁴⁰. A perhaps more relevant observation is that the changes in three schedules (IV)^{18,199} or the starting or

stopping of night work^{147,200} in all five instances led to changes in biomarkers of IHD in the predicted direction. The changes were however not very homogenously with some relating to triglycerides, others to HDL-cholesterol or total cholesterol, and for all studies with inadequate controlling for dietary changes in parallel with the interventions.

Analogy: There are no tempting analogies in the literature stress being a possible exception, but as pointed out by Rothman and Greenland analogies might be handicapped by “the intensive imagination of scientists, who can find analogies everywhere” (p. 27)

In summary, the evidence for a causal relation between shift work and IHD is perhaps on balance unsettled but mostly tilting in favour of a relation. The experimental evidence in five studies and the sharp rise with a longer exposure would favour the relationship, while the relatively low strength and the lack of consistency would be counting against. The evidence at the same time is heavily dependent on few studies with the most crucial⁷ building on only 43 IHD cases. The larger epidemiological studies (including II) are not methodological as good and the area still needs good epidemiological studies in order to settle the question. The crucial problems are exposure assessment, control of selection, controlling relevant confounders, especially social class and work environment, and comparing with a more relevant control group.

Is it a causal risk factor for all?

Taking the balance in favour of a causal risk factor the metaanalysis¹¹⁵ suggests that shift work would only be a risk factor in some situations. Thus, it might be that shift work were only a riskfactor for some of the exposed workers or for exposed workers in cer-

tain situations.

If stress in the Lazarus sense is involved shift work might only be a risk for some people. Some shift workers regard their shift work as not being particular problematic, they sleep well, are comfortable with their working hours, and would not want it any other way around. It has been used to propose that shift work should be reserved for those choosing it for themselves. It might be that if shift work were not perceived as stressful then the risk of IHD would not be higher for them. It might explain the heterogeneity of the epidemiological literature but it has not been examined in relation to IHD or biomarkers.

Shift work could also be a risk factor only when interacting with other known risk factors. In a Finnish study²⁴¹ shift work had a superadditive effect on BMI and smoking, leading to a relative risk of 2.7 (1.8-4.1) for shift work and smoking (the risk for non smoking shift workers 1.6 and for day working smokers being 1.3, both compared with non smoking day workers) and for shift work and overweight 2.3 (1.5-3.6) with the basal risks being 1.2 and 1.3. This might suggest

that shift work would be a risk factor especially for those being obese or smokers. In an yet unpublished study[15] from the SHEEP-VIP case-referent study we repeated the analyses and found that while smoking and BMI did not act superadditively in this study, WHR had a significantly superadditive effect in women and physical inactivity was superadditive in both genders. This question is thus also still unanswered.

Another type of explanation of a selective risk would be related to the place and time of the study. It would as previously described be possible that some shift workers were forced to work nights as other jobs were not available for them. Thus, the societal background could force some reluctant workers to a work pattern including night work against their wishes. These shift workers could in theory have a higher risk while self selected and well adapted had no additional risk. This has not been investigated either.

[15] Bøggild, Knutsson, Nilsson, Hallquist, Reuterwall. Combined effects of shift work and lifestyle factors on risk of myocardial infarction in the SHEEP/VIP study. Unpublished

Table 5. Exposure information in studies on shift work, risk factors, biomarkers and IHD

First author, year	Shift work exposure definition
Alfredsson 1985 ⁶	Aggregated if reported by 50% in other study: irregular working hours
Alfredsson 1982 ⁵	Aggregated if reported by 50% in other study: continuously changing day and night work schedule
Angersbach 1980 ¹¹⁹	> ½ year on either (90%) (1): DN--DN-/DN--DN--DN--D/N--DN-/ or (10%) (2): DN-DN--/N-DN-DN-/DN-D--/ (D: 6.00-18.30; N: 18-6.30)
Baumgart 1989 ¹³⁷	Eight hour (three shift), weekly rotation with weekends off
Bursey 1990 ²¹⁶	> five year in shift. Three shift, eight hour.
Bøggild 1999 (II)	Prevalent, irregular working hours, shift work, often night work
Cesana 1985 ¹⁵⁷	Weekly rotating shift
Cesana 1990 ²¹⁷	Rotating and permanent night workers
Chau 1989 ¹³³	DDAANN-- (D: 4.00-12.00; A: 12.00-20.00; N: 20.00-04.00)
Costa 1990 ²¹⁸	Not stated
De Backer 1987 ²¹⁹	Three shift system
Fouriaud 1984 ²¹³	Work site physician: shift work, irregular schedules
Fredén 1984 ²⁴²	Not stated
Gordon 1986 ²¹²	Does your job involve a variable work shift. That is, do you work the day shift sometime and the night shift at other time
Kawachi 1995 ¹¹⁶	> 1 year of > 3 nights a month (rotating)
Kecklund 1994 ¹⁹⁹	Old: AAAAAAA--DDD--/DD--FFF/FFFF---/---NNNN/NNN----/ New: AAAANN--/DDD--/DD--AAA/NNNN---/FFFFFFF/-----/ (D: 7.15-15.45; F: 7.00-15.00; A: 15.00-23.00; N: 23.00-7.00)
Knutsson 1986 ⁷	> 6 month: Before 1975: (1) DDAAAAD*/--DDDD-/NN--NNNN*/AANN---/, after 1975: (2) NNNN---/DD-AAAD*/--DDDD-/AAA-NNNN*/ (D: 6.00, A: 14.00, N: 22.00, *=12 hour shift)
Knutsson 1988 ²⁰⁸	(3): NNNN---/DD-AAAD/--DDDD-/AA-NNN-/-----/ (4): DDDDAAA/A-NNNN-/-----/ (5): DD-AAAD/-----/AAA-NNN/--DDDD-/NNNN---/ (D: 6.00, A: 14.00, N: 22.00)
Knutsson 1989 ²²⁰	As Knutsson 1988
Knutsson 1990 ¹⁴⁷	As Knutsson 1988 (3)
Knutsson 1999 ¹¹⁷	Did you undertake shiftwork (during the last 5 years), if yes: type of schedule. (and) when was the major part of your work hours scheduled (6-18, 18-22, 22-6)?

First author, year	Shift work exposure definition
Koller 1983 ²⁴³	ANN---/-DDDDDN/N--AAN-/MAANN-/MAANN-D*/ANN---/-DDDDD*N/N--AANN/N--AAN-/DAANN-D*/ANN---/-DDDDD*-/-DDDDD*N/N--AAN-/DAANN-D*/ANN---D*/ D:6.50-13.50; A:13.50-20.50; N:20.50-6.50; D*6.50-20.50
Lang 1988 ²⁴⁴	Work site physician, employees, visits: shift work
Lasfargues 1996 ²²¹	Night workers
Lennernäs 1994 ¹⁴⁶	DDDDD-/AAAAA--/NNNN---/ (D: 5.30-14.00, A:14.00-22.30; N:22.30-5.30)
McNamee 1996 ¹²⁰	>1 month, one week forward rotation
Michel-Briand 1980 ²⁴⁵	Shift work
Nakamura 1997 ⁸⁶	> 3 years, DDDD-AAAA-NNNN-- (D: 8.15-15.15; A:15.15-22.30; N: 22.30-8.15)
Netterstrøm 1996 ²²²	Not stated
Orth-Gomér 1983 ¹⁸	Counter clockwise: 22.00-07.00; 18.00-02.00;14.00-22.00;10.00-18.00; 07.00-14.00; - ; - /, Clockwise: 7.00-14.00; 10.00-18.00; 14.00-22.00; 18.00-02.00; 22.00-07.00; - ; - /
Peacock 1983 ²⁴⁶	Old system: NNN*AAMMM-----, New system: nn-dd--- M: 08.00-16.00, A: 16.00-24.00, N: 24.00-08.00. N*: 24.00-08.00 and 16.00-24.00, d: 07.00-19.00, n:19.00-07.00
Peternel 1990 ²²³	Three shift rotation, 7 days between shifting. 6-14, 14-22, 22-6
Romon 1992 ²²⁴	MMAANN---/ 6-14, 14-22, 22-6
Steenland 1996 ¹²¹	Prevalent night shift
Sundberg 1987 ¹³⁹	MMMM and NNNN ? M: 7-15, N: 21.30-7.30
Taylor 1972 ⁴	Three shift, weekly rotation; three shift, faster rotation; alternating day and night; double days; rotating 12-hour shift; regular night work.
Tenkanen 1997 ¹¹⁸	Mostly MMMM-AAAA-NNNN-----, 20 weeks schedule (?), or MMAANN-----. Exposure relies on questionnaire data: part-time, two shift, three shift, irregular night work
Thelle 1976 ²²⁵	Not stated
Theorell 1976 ²²⁶	Three weeks of fixed night shift (?) 22.30-7.30, three weeks of day 7.30-16.30
Thiis-Evensen 1949 ²	Not stated

First author, year	Shift work exposure definition
Tüchsen 1993 ¹⁷⁷	Aggregated if reported by 20% in other study. Night and morning work (bakers), late evening (taxi operators, transport, hotels, restaurants and cafés, cooks, waiters), 24-hour work (fishermen, traffic staff, shipmaster, railway staff, bus, coach, road transport, rescue services, customs, excise, police), other irregular work (dataprocessing, doormen, ticket-checkers, marshals, security staff, drivers, production workers, wage-earners not elsewhere classified).
Åkerstedt 1987 ²⁰⁹	Aggregated if reported by 20% in other study: Night work.
Morikawa 1999 ¹⁵⁸	2/3: DDDDD--/NNNNN--/AAAAA--, 1/3 DDDD-NNNN-AAAA- or DDD-NNN-AAA- (D: 8.00-, A: 16.30- N: 00.15- or 6.30, 13.00 and 21.30)
Murata 1999 ¹⁶¹	Four shifts, 1 day off, forward rotation
Aanonsen 1964 ³	NNNNNN-/MMMMMM-/AAAAAA- or MM-----/AAAAAAM*/- MMMMMA/NNNNNNA/M-MM---/AAAAAAA-/MMMMM-/NNNNNNA/M---MM- /AAAAAAM*/-MMMMM-/NNNN-NNA/ (M*: morning and night shift same day)

Table 9. RRPA scores and extracted information from studies of shift work, biomarkers and IHD, giving full information on shift schedule (schedules are shown in table 5)

	Angersbach (1)	Angersbach (2)	Chau	Kecklund (old)	Kecklund (new)	Knutsson (1)	Knutsson (2)	Knutsson (3)	Knutsson (4)	Knutsson (5)	Koller	Lennernäs	Nakamura	Orth-gomér (ccr)	Orth-gomér (cr)	Peacock (old)	Peacock (new)	Romon
Regularity (comb.)	7.0	6.9	7.9	8.5	8.1	8.0	8.4	8.5	8.3	8.2	7.8	8.8	8.4	5.9	5.9	8.0	8.1	7.5
Periodicity	8.3	8.0	7.7	5.4	6.8	6.4	6.2	6.3	6.3	6.3	7.2	6.2	5.6	8.0	8.8	7.2	7.6	7.7
Load shift	4.7	4.7	8.0	7.9	7.9	7.6	7.6	8.0	8.0	8.0	7.3	7.9	7.8	7.9	7.9	7.1	5.1	8.0
Load week	7.4	6.6	7.7	8.2	8.2	7.6	8.3	8.4	8.2	8.4	7.5	8.1	7.6	8.0	8.0	7.9	7.6	8.1
Opport rest night	7.5	7.1	7.7	8.1	8.2	7.5	8.0	8.0	8.1	8.0	7.6	8.0	7.4	8.4	8.4	7.8	7.7	7.9
Predictability	8.9	8.8	8.1	4.6	5.1	5.0	3.3	5.6	7.2	5.6	2.2	7.5	4.6	8.4	8.4	6.0	7.2	6.9
Opport household act	7.5	6.7	7.6	7.1	7.1	7.6	8.0	8.0	7.8	8.0	7.6	6.7	7.6	6.9	6.9	7.7	7.6	7.9
Opport evening recr.	7.6	6.8	7.6	8.1	8.2	7.5	8.0	8.0	8.5	8.0	7.5	6.6	7.5	6.4	6.4	6.9	7.6	7.8
Opport weekend recr.	1.5	5.0	0.8	5.5	5.5	4.0	4.4	4.4	4.0	4.9	3.1	10.0	2.7	10.0	3.0	5.5	3.0	3.3
worktime/w	43.8	50	42	35.1	35.1	42	33.6	32	32	32	41.6	37.7	42	40	40	36	42	37.8
operating time	172	148	168	168	168	168	168	168	112	168	168	113	168	40	40	56	168	168
hour 22-06	56	48	112	56	56	56	56	56	32	56	224	33	224	12	12	24	112	112
< 11 hours off	0	0	0	0	0	2	1	1	0	1	0	0	0	0	0	1	0	0
< 36 hours off	0	5	0	0	0	0	0	0	0	0	6	0	0	0	0	0	7	0
free sunday in rota	1	2	1	3	3	2	3	3	1	3	5	3	4	1	1	1	3	3
max nbr of night/row	1	1	2	7	4	3	3	3	4	4	3	4	4	.	.	3	2	2
nbr of night shifts in rota	7	6	16	7	7	7	7	7	4	7	28	4	28	.	.	3	14	14
max nbr of evening/row	.	.	2	7	4	4	3	3	4	3	2	5	4	.	.	2	.	2
nbr of evening shifts in rota	.	.	16	7	7	6	6	6	4	6	20	5	28	.	.	2	.	14
shift length	12	12	8	8	8	8/12	8/12	8	8	8	8/12	8	8/10	8	8	8	12	8
number of shifts	2	2	3	4	4	5	5	3	3	3	4	3	3	5	5	4	2	3
length of rota	4	3	8	6	6	4	5	5	3	5	16	3	16	1	1	2	8	9
hour 22-06/week	14	16	14	9.3	9.3	14	11.2	11.2	10.6	11.2	14	11	14	12	12	12	14	12.4

Conclusion and perspectives

In conclusion

- the studies suggests that although social class and work environment differs between shift and day workers shift work could be a causal risk factor for IHD especially as intervention towards ergonomically better schedules change biomarkers of IHD and as different shift characteristics as the amount of night work are related to biomarkers.
- By changing shift schedules in accordance with ergonomic criterias introducing regularity and predictability the lipid biomarkers of IHD were changed in the predicted direction.
- Shift work, night work, and especially the number of hours worked between 22 and 6 among night workers, were associated to lipid biomarkers and glycated hemoglobin. Regularity and perodicity were also associated as predicted, regardless of whether exposure was taken as the result of the intervention or regardless of this.
- In general, except for glycated hemoglobin neither the stress biomarkers nor questionnaire data were associated with shift work but an unsolved problem is that the stress of shift work is not very theoretical understood.

Shift work as a risk factor for IHD

On balance shift work seems to be a causal risk factor for IHD. Some comments should however be given.

With regard to the causal chains that must be connecting shift work with IHD the literature has been concentrating on lifestyle factors, and although they did not have impact in the intervention study it might be that smoking

and especially diet could be responsible for the association. This would not mean that shift work was not leading to IHD, but merely that the timing of eating was acting as a mediating factor. It would, however, be important to know in relation to prevention strategies. The results of the intervention studies suggests that causality via diet is less probable.

In contrast, not much has been done to evaluate other possible causal pathways especially relating to circadian disruption and stress. For the latter, both sleeping and domestic problems have been described at numerous occasions and it is surprisingly what little focus has been on these agendas in relation to risk of IHD or biomarkers.

The population impact of shift work on IHD was evaluated by Olsen and Kristensen⁷² suggesting a attributable risk of 7% for both men and women. This might be to high. I suggested the risk to encompass only part of the exposed population although the precise mechanisms is not known, and as the risk might be related only to shift work encompassing certain characteristics as for instance night work the number of exposed people might also be lower than assumed in the calculations by Olsen and Kristensen. In population III, 3.6% of the employees had night work, 4.8% evening or two shift work, and 10.4% other types of irregular working hours. This could mean that the exposed group could be below 5% (in relation to risk of IHD).

For the exercise, the exposed population is set at 5%, 50% of whom are regarded as sensitive and the result of the metaanalysis¹¹⁵ is used as the relative risk (1.3). This leads to an attributable risk of $(1.3 - 1) * 0.5 * 0.05 / ((1.3 - 1) * ((0.5 * 0.05) + 1))$ or 2.4%. Besides the unsecurity of the figures in the

calculations aetiological fractions has the problem of assuming that the causes of disease are unrelated which is probably not the case for IHD.

Relating to the biomarkers a 15% reduction in for instance total/HDL-cholesterol following an ergonomically better schedule (IV) would have potential impact on the exposed shift working population as the distribution of cholesterol in the population would shift²⁴⁷.

Even so, the potential benefit of prevention could be larger as other negative effects of shift work are also considered to be preventable by changing the risk of IHD although nothing is known on the schedule characteristics and for instance gastrointestinal disease.

Future research

The research perspectives were described in publication I but a few highlights are relevant in relation to the discussion in this thesis.

There is still a need for well conducted epidemiological studies. They would however need to be better planned if results should be less open for debate. First and foremost the populations should be much better defined in terms of exposure and especially thorough selection of the control group should be given high priority. It might not necessarily be day workers but could be for instance two shift workers or workers with a less demanding schedule (taking advantage of for instance the RRPA or other ways of describing the schedule) in order to secure a reference group that is more closely resembling the shift workers (except on the shift work).

Controlling should be done on age, gender, social class, and work environment factors. The possibility to control also for personality factors as hostility should be considered. The

effects of sleep deprivation, social disruption, and shift work related stress in relation to IHD should be given priority in order to fill the gaps in knowledge on the web of causation.

Information on lifestyle factors should be treated as both confounders and mediating variables and multivariate models should be presented both with and without these.

Information on biomarkers should normally be considered mediating factors, especially lipids and blood pressure that could be mediating a higher risk.

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, preferable the schedules worked in.

The biomarker studies should preferable be more precise in their measuring, either ensuring that participants are at day orientation or that they measure several samples a day in order to obtain information on the circadian phase. New markers might be useful, especially in relation to hemostasis^{54,87} and stress¹¹⁰. The description of timing and kinetics of markers should be given priority.

Further work on definition of shift work exposure assessment should be made eventually in terms of “integrated lifetime hours of night shift work”.

Preventive perspectives

How could the information from publication IV and V be used in prevention?

The results show that the shift schedule is associated with biomarker levels. Schedules that follows the ergonomic criterias lowers biomarkers thus potentially leading to lower r

isk of IHD. In the NARFE II study a more regular and predictable schedule led to better biomarkers. The schedules were very irregular from the outset, and as the wards were self selected it might not be a random sample of shift systems in Danish hospitals. Other schedules might be more regular and it would be relevant to test changes in other settings.

In a study on 402 German industrial and service sector schedules Gissel and Knauth²⁴⁸ found that many of the schedules could be improved from an ergonomically point of view. It seems plausible that this situation would not be very different in Denmark, although information on Danish shift schedules are not available.

The other schedule characteristics of relevance is that the number of night shift hours were associated with biomarkers among night workers. This suggests that the lowest risk would be obtained by spreading out the night shift hours on more people in order to have the lowest change in distribution. I should note though, that we had only 6 fixed night shift workers in the analysis, and this area would be very relevant to pursue.

On the other hand, changes in society calls for more flexibility, both on behalf of the employers (possibility of having people working at short notice, in schedules changing with market and production²⁴⁹, lean production, production on demand et cetera) and on behalf of the employees who wishes for flexible shift scheduling in order to obtain autonomous organisation of social and domestic life²⁴⁹. The labour market may become more segregated with people having long term contracts with individual flexibility and short term employees having to work when work is needed. This might give rise to more pronounced social differences in working hour conditions.

The result of publication IV suggest that although flexibility is judged highly positive it should be followed by regularity. This will necessarily mean that employers, cooperation committees and health and safety committees, as well as the employees themselves will have to put up rules for the scheduling of both shift and other flexible types of work schedules in order to maintain regularity in the growing demand for flexibility.

Abstract

Work situated outside normal day working hours is the condition for many employees. These shift working hours have been related to heart disease for the last 15 years but with studies not finding a higher risk. Several methodological problems have been described, and it was the aim of this thesis to examine whether shift work could be regarded as a causal risk factor for ischemic heart disease (IHD).

The epidemiological literature have been extensively reviewed, and possible causal links discussed. The problem is attacked from two points: Two publications discusses the effect of social class and work environment factors, both risk factors for IHD. Both confounders are heavily screwed between day and shift workers, and have potential impact on the measured relationship between shift work and IHD. The second point comprised of a intervention in shift scheduling aiming at more ergonomic schedules. The intervention at four hospital wards succeeded in changing the schedules, and in parallel with this biochemical risk factors (biomarkers) changed towards lower values. The baseline figures were utilised to examine the effect of different characteristics of shift

work and showed that especially night work and among night workers the amount of night work (given as hours between 10 pm and 6 am in an eight week period) was associated to higher biomarkers of IHD, especially triglycerides and HDL-cholesterol. Stress biomarkers were in general neither changing nor associated to characteristics, with the exception of glycated hemoglobin that was higher among shift workers.

The thesis discusses confounding and exposure characteristics and concludes, that shift work is probably a causal risk factor raising the risk by 30-40%, but with the possibility that shift work is interacting with unknown factors so that in some instances the risk is not raised.

The demonstration that shift scheduling can influence biomarkers of IHD suggests that shift work associated IHD may be prevented by using knowledge on circadian rhythmicity and social preferences, as suggested by several lists of ergonomic scheduling. The publications in this thesis suggests, that especially regularity of schedules and the amount of night shift work is relevant for prevention.

Resumé

Arbejde udenfor normal dagtid er hverdag for mange ansatte. Disse skiftarbejdstider har været relateret til udvikling af hjertesygdom. Litteraturen er imidlertid behæftet med mange metodemæssige problemer, og det var målet med denne afhandling at undersøge om skiftarbejde kunne betragtes er en kausal årsag til iskæmisk hjertesygdom (IHS)

Den epidemiologiske litteratur er grundigt gennemgået og mulige kausale årsager diskuteret. Afhandlingen angriber problemstillingen fra to sider: I to publikationer undersøges effekten af forskelle i social klasse og forekomsten af andre arbejdsmiljøfaktorer mellem dag og skiftarbejdere på risikoen. Begge potentielle konfoundere var skævt fordelt mellem grupperne og kunne være af betydning. Det andet angrebspunkt bestod af en kontrolleret intervention i planlægningen af skift arbejde med henblik på indførelse af mere ergonomisk planlagte arbejdstidssystemer. Interventionen på fire sygehusafdelinger medførte arbejdstidssystemer der var mere regelmæssige og parallelt hermed ændredes kolesterol og lipoprotein (biokemiske risikofaktorer (biomarkører) for IHS) i retning af lavere værdier.

Ved analyse af tværsnitsdata fra indgangen til interventionsundersøgelsen fandtes sammenhæng mellem karakteristika ved skiftsystemet og biomarkører. Der fandtes sammenhæng

mellem skift arbejde og højere biomarkører (særligt triglycerid og HDL-kolesterol), og særligt natarbejde og blandt natarbejderne omfanget af natarbejde (udtrykt som antal timer mellem 22 og 6 på otte ugers vagtplan) og højere biomarkører for IHS.

Bortset fra glykeret hæmoglobin var biomarkører for stress ikke associeret til interventionen eller til karakteristika ved arbejdstidssystemet.

Afhandlingen diskuterer konfounding og eksponeringskarakterisering for skiftarbejde, og konkluderer at skiftarbejde formentlig er en kausal risikofaktor med en øget risiko på 30-40%. Der er dog mulighed for at skiftarbejde interagerer med andre ukendte risikofaktorer, og at risici kun er øget i visse situationer.

Påvisningen af at skiftsystemets udformning har betydning for niveauet af biomarkører for IHS medfører en anbefaling af at en skiftassocieret risiko for IHS kan forebygges gennem ergonomiske principper for skiftsystemets opbygning. Disse principper, der bl.a. bygger på viden om circadiane rytmer og sociale ønsker findes i flere versioner. I artiklerne der hører til denne afhandling er det særligt betydningen af regelmæssighed og omfanget af natarbejde, der er relevant for forebyggelse.

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