METABOLIC DISTURBANCES IN SHIFT WORKERS

Berndt Karlsson

Umeå 2004
You learn from a conglomeration of the incredible past
– whatever experience gotten in any way whatsoever.

Bob Dylan
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ABSTRACT
METABOLIC DISTURBANCES IN SHIFT WORKERS

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An increased risk for coronary heart disease among shift workers is earlier shown in the epidemiological literature. The aim of this thesis has been to penetrate metabolic disturbances and obesity among shift workers compared to day workers, and to compare if there are differences in total mortality or cause specific mortality of coronary heart disease (CHD), diabetes or ischaemic stroke in between the two groups.

In an intervention study on female nurses (N=11), on night schedules in Umeå hospital, the highest peak value of glucose and insulin after meal ingestion was seen in the late evening (23:30). The post-prandial area under curve (AUC) of glucose and insulin was correspondingly largest after meal ingestion the same clock hour compared to meal ingestion other clock times.

In two different cross-sectional studies Västerbotten Inventory Study (VIP) (N= 27,485) and in a subset of Work, Lipids and Fibrinogen Study (WOLF) (N= 1,324) metabolic differences in between shift and day workers has been evaluated. In both studies have obesity, high triglycerides and low HDL-cholesterol been more prevalent among the shift-working group compared to the day-working group. After adjustments for age and socio-economic factors in the VIP-study obesity and high triglycerides remained as risk factors in shift workers in both men and women. After directly age standardisation, a clustering effect, simultaneously, of two or more metabolic risk factors (obesity, hypertension, and high triglycerides) was seen in both genders among the shift workers compared to the day workers. Correspondingly, in the Wolf study low HDL-cholesterol and high triglycerides remained as significant risk factors after adjustments of confounders as age, socio-economic group, physical activity, current smoking, low social support and high job strain.
In a cohort study from one company (MoDo) with two plants in the pulp and paper industry 2,354 male shift workers and 3,088 male day workers were followed from January 1, 1952 to December 31, 2001 regarding total and cause specific mortality due to CHD, diabetes and ischaemic stroke. Groups of workers defined by different duration of shift exposure were compared with day workers by calculating standardised relative rates (SRR).

No increased risk of total mortality was seen among shift workers compared to day workers. Higher duration of shift work was associated with increased risk for CHD, and shift workers with 30 years or more had the highest risk. Diabetes was more common with increasing number of shift year exposure. Compared to day workers shift workers had also an increased risk to die because of ischaemic stroke, with the highest relative difference in the least shift exposed group (< 5 years).

Keywords: shift work, epidemiology, mortality, diabetes, stroke, coronary heart disease, obesity, triglycerides, HDL-cholesterol, insulin, glucose
This thesis is based on the following papers, which will be referred to by corresponding Roman numerals:


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INTRODUCTION

"Shiftwork" or "shift work"? Which term is correct? Some experts prefer the former, others the latter. Professors of semantics could probably spend an evening debating the issue over dinner. But the issues raised in this thesis are infinitely more complicated. At the risk of sounding a little grandiose, it is no less than an attempt to understand how the movement of our planet around the sun affects the wellbeing and function of the most complicated of all organisms – the human being - in that most complicated of environments – the workplace.

Throughout history nature has governed the timing of human work. Lack of adequate light has always been the greatest limitation, and the invention of electric light changed the workplace radically. Shift work was initially confined to industry, but in today's globalised "24-hour society" almost all forms of work can involve working shifts.

The studies presented in this thesis consider long-term aspects of shift work exposure from early beginnings to modern shift patterns in the industrial and service sectors. Do these studies contain new implications for the health of shift workers? When they are considered together, they shed some light on both total and cause-specific mortality and also highlight the metabolic issues raised by shift work exposure.
BACKGROUND

SHIFT WORK

According to the European Directive Standard, implemented in Swedish law, shift work is defined as a method that divides work into shifts, whereby employees relieve each other at the same workplace according to a certain organisational pattern that may rotate. Shifts may be continuous or discontinuous and may involve working at different times during the day or night over a given period of days or weeks. A shift worker is defined in the directive as an employee whose work schedule includes varying working hours (European Council 1993).

Shift patterns have been organised in various ways, often governed by local traditions. In Swedish society, attitudes to shift schedules vary. Workers have been able to choose from many schedules suited to their particular organisation, and despite scientific evidence of the adverse effects of shift exposure, new and healthier schedules have not always been readily accepted. The ordinary worker has tended to say "better the devil you know than the devil you don't". Swedish trade unions have negotiated local agreements on work schedule arrangements which have pre-empted the non-statutory changes to working hours contained in the Working Hours Act (Regeringskansliet 1982).

New legislation led to the gradual reduction of the Swedish working week from 48 hours in the 1950:s to about 40 hours by the 70:s. For some groups of workers, especially shift workers, working hours were reduced even further. Nowadays, fully employed shift workers often have a 36-hour week. The last reduction from 40 to 36 hours a week was the result of local agreements between employers and employees.

According to the third and the most recent European Union (EU) Survey on Working Conditions (Boisard, Cartron et al. 2002) only 24% of the working population now works according to a "normal" or "standard" daytime schedule, i.e. between 07:30-08:00 and 17:00-18:00 from Monday to Friday. The other employees have work patterns that include shift and night work, part-time work, weekend work, split shifts, compressed work, varying working hours, seasonal work, and on-call work (Costa 2003). The same European statistics (Boisard, Cartron et al. 2002) show that of the various possible shift systems,
alternating day - i.e. morning and afternoon shifts - is the most common, but 18.8% of the workforce is engaged in shift work that includes night work - 24% of men and 12% of women. Seven percent of shift workers work nights permanently.

HEALTH ISSUES IN A 24/7 SOCIETY

With increasing economic and social demands, we are rapidly evolving into a 24-hour society. Poor sleep, gastrointestinal problems, higher accident rates and social problems represent short-term effects. The long-term effects of modern 24-h society, however, are more uncertain (Rajaratnam and Arendt 2001).

Reports on the impact of shift work on health and wellbeing have however increased during the past decades (Harrington 1994; Costa 1996; Akerstedt 2003; Costa 2003; Folkard and Tucker 2003; Knauth and Hornberger 2003; Knutsson 2003). The more long-term health aspects of shift work are by definition more difficult to identify and evaluate, but they are, rightly, becoming the subject of greater attention (Knutsson 2003).

Similar concerns had led the International Labour Organization (ILO) to make recommendations in 1990, and in 1993 the European Council issued a directive which is binding within the European Union. These regulations apply to all forms of organised work, but a number of points are directly applicable to shift work. The ILO recommendations require the employer to: (I) advise the worker regularly on how to cope with shift work, (II) transfer the worker to similar day work if the worker is unfit for shift work, (III) give specific rewards for shift work, (IV) consult the employee about the details of the shift work, and (V) ensure at least 11 hours of rest in each 24-hour period (International Labour Office 1990). The European Directive is similar. It calls for (I) a minimum daily rest period of 11 hours in a 24-hour period, (II) a rest of at least 35 consecutive hours per seven-day period, (III) a maximum of 48 working hours per week, and (IV) transferal to day work when problems with night work are evident (European Council 1993).

An ideal shift system does not exist, but in a recent review article by Knauth and Hornberger, measures that can optimise the wellbeing of shift workers and even to identify ill health at an early stage were highlighted (Knauth and Hornberger 2003).
Background

The Swedish National Board of Occupational Safety and Health issued special recommendations for medical surveillance in relation to the above recommendations (The Swedish National Board of Occupational Safety and Health 1997). Under Swedish legislation, the definition of a "night worker" is so strict that only about 80,000 individuals are entitled to a health examination. This legislation covers individuals that work at least three hours of a shift during "primary night hours", i.e. 00:00-05:00, or have 38% of a whole year’s working time confined to these primary night hours.

Swedish guidelines for health checks in night workers are considered to be less strict and less ambitious than the general guidelines recommended by Costa (Costa 1998; Costa 2003).

PRESENT GUIDELINES AND RECOMMENDATIONS GOVERNING MEDICAL SURVEILLANCE OF SHIFT WORKERS.

Costa highlighted the importance of the "occupational health physician", who should evaluate workers' fitness for shift work and night work prior to employment, at regular intervals, and in cases of "health problems connected with night work" (p, 151) (Costa 1998). He also suggested a validation of shift schedules according to ergonomic criteria. Early signs of reduced tolerance to shift work such as sleep and digestive problems or increasing consumption of medicines, increased accidents, and impairment of reproductive function are looked upon as alarm signals of shift work intolerance. Shift workers are entitled to clear information about the possible negative effects of shift work and should be counselled about coping with shift and night work.

HEALTH EFFECTS OF SHIFT WORK

Accidents

Efficiency and safety are two sides of the same coin. Well-known accidents, e.g. the Three Mile Island and the Chernobyl accidents occurred at night and put the issue of sleepiness as a risk factor for accidents into focus. In a newly published review article, Folkard and Tucker presented a number of trends in productivity and safety
Background

(Folkard and Tucker 2003). (I) The relative risk of accidents increased across morning (reference), afternoon (18.3%) and night shift (30.4%). (II) The relative risk increased over four successive night shifts, first (reference), second (6%), third (17%) and fourth (36%) (III). Risk increased in an approximately exponential fashion with time on shift, so that by the twelfth hour it was more than double that found during the first 8 hours (IV). Risk rose substantially and approximately linearly, between successive breaks so that risk doubled during the last 30-minute period before the next break. The reduction of safety reflects a number of underlying factors, including impaired health, disturbed social life, shortened and disturbed sleep, and disrupted circadian rhythms.

Sleep problems

Shift workers practically always report more sleep disturbances than day workers. The effects vary, however, depending on shift timing. The impact on sleep pattern is different with night, morning and afternoon shift schedules (Akerstedt 2003). Night work and early morning shifts have the most negative impact on sleep patterns. Day sleep is short after night work due to the circadian rhythm. Involuntary sleep occurs during night shifts, and an afternoon nap sometimes compensates for shortened day sleep. The sleep pattern before an early morning shift appears to be even more disturbed with reduced sleep duration compared with the sleep pattern of the night shift (Folkard and Barton 1993). The main subjective effect is a pronounced difficulty in waking early, which is why morning shifts are typically the most unpopular of the three shifts (Akerstedt 2003).

Gastrointestinal disease

Gastrointestinal disorders are more common in shift workers than in day workers (Scott and Ladou 1994). Harrington (Harrington 1978) and This- Evensen (This-Evensen 1949) called ulcers "the occupational disease of shift workers". Peptic ulcer disease may well be underestimated as many ulcers are asymptomatic. In a highly regarded Japanese study, ulcer diagnoses were verified endoscopically in 11 657 employees with abnormal radiological findings (Segawa, Nakazawa et al. 1987). This study showed that the prevalence of
Background

gastric and duodenal ulcers in shift workers (2.38% and 1.36% ) was nearly twice that of day workers (1.36% and 0.69%).

Pregnancy

There is quite strong evidence supporting an association between shift work and pregnancy outcome in terms of miscarriage, low birth weight and preterm birth (Knutsson 2003). In the same review the author concluded that "in the absence of further proof, it would be prudent for women to avoid or be relieved of such work during pregnancy" (p 106).

Cancer

No detailed study of shift work as a major cause of cancer has been carried out. However, the results from a study by Taylor and Pocock indicated that tumours were commoner in shift workers than in the general population (SMR =116) (Taylor and Pocock 1972; Knutsson 2003).

During recent years, six studies have shown increased risk of breast cancer in female shift workers (Tynes, Hannevik et al. 1996; Davis, Mirick et al. 2001; Hansen 2001; Hansen 2001; Kliukiene, Tynes et al. 2001; Schernhammer, Laden et al. 2001).

The biological mechanism for this effect is assumed to be the suppression of normal nocturnal melatonin production in the pineal gland due to exposure to light during the night (Glickman, Levin et al. 2002; Poole 2002). Melatonin was earlier thought to downregulate circulating levels of gonadal steroids, but melatonin could act directly through other mechanisms on tumour cells or through its antioxidant or immuno-enhancing properties (Cos and Sanchez-Barcelo 2000).

Cardiovascular disease (CVD)

Cardiovascular diseases are perhaps the most studied outcomes in connection with shift and night work. In a recent review article, Bøggild and Knutsson presented a summary of 17 studies (Bøggild and Knutsson 1999). In general, shift work was associated with a 40% increase in risk of cardiovascular morbidity and mortality. Of the
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cohort studies, two (Taylor and Pocock 1972; Bøggild, Suadicani et al. 1999) did not show any increased risk in shift workers, but the other seven did indicate an increased risk of CVD (Angersbach, Knauth et al. 1980; Alfredsson, Spetz et al. 1985; Knutsson, Åkerstedt et al. 1986; Åkerstedt, Alfredsson et al. 1987; Tuchsen 1993; Kawachi, Colditz et al. 1995; Tenkanen, Sjöblom et al. 1997). Of the four cross-sectional studies, three showed an elevation in CVD risk (This-Evensen 1949; Michel-Briand, Chopard et al. 1980; Koller 1983) and one did not (Aanonsen 1964). Of the four case-reference studies the risk estimate for CVD was elevated in two (Alfredsson, Karasek et al. 1982; Knutsson, Hallquist et al. 1999), but unchanged in the other two (McNamee, Binks et al. 1996; Steenland and Fine 1996).

General Mortality and Cause-Specific Mortality

All-cause mortality among shift workers has been reported only in few internationally published papers. Taylor and Pocock (Taylor and Pocock 1972) followed a cohort of 8603 male manual workers in England and Wales from 1956 to 1968. The workers were subdivided into day workers, shift workers and ex-shift workers. Mortality was compared with the general population for each group, and observed and expected number of deaths were reported. Internal comparisons were not done, but SMRs can be calculated from the data. The SMR for all-cause deaths were 97, 101, and 119 for day workers, shift workers and ex-shift workers respectively. The results indicate a moderate excess of mortality in shift workers, if shift workers and ex-shift workers are combined. Mortality may well be over-represented in ex-shift workers as many would have discontinued shift work on grounds of ill-health. The authors conclude that "shift work would appear to have no adverse effect upon mortality".

In the Copenhagen male study, (Bøggild, Suadicani et al. 1999) a Danish cohort of 4804 day workers and 1123 shift workers were identified and followed up for 22 years, (from 1971 until 1993) through hospital discharge registers for ischaemic heart disease (IHD), and cause of death was recovered from death certificates.

The main advantage of this cohort study is the possibility of compensating for potential confounders. The all-cause mortality risk comparing shift and day workers, when adjusting for age and social class was 1.1 (CI 0.9-1.3). With further adjustments, including sleep
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deviation from 6-7h/day, tobacco use, weight, height and fitness value, the all-cause mortality risk ratio for shift versus day workers was 0.9 (CI 0.8- 1.1).

In three Norwegian chemical plants (This-Evensen 1949) a cohort of 1 390 male employees was followed from 1918-19 to 1948. During this time 803 persons died (498 day workers, 212 shift workers and 93 workers who had worked both days and shifts). Since the denominator is not reported, it is not possible to calculate cumulative incidence in the three subgroups. However, it is quite possible to calculate the proportionate mortality ratio (PMR) from the data. The PMR from cardiovascular disease was 1.36 in shift workers compared to day workers, and the PMR for the malignancies and tuberculosis were 1.14 and 1.22, respectively.

Steenland et al carried out a nested case-control study of 163 men and 781 controls in a population of 21 491 male workers at four heavy equipment plants (Steenland and Fine 1996). After adjustment for age, race and plant, they could not show any significant association between shift pattern or recent change of shift pattern and cardiovascular death.

METABOLIC EFFECTS OF SHIFT WORK

“Normal physiology in short” with focus on plasma lipids, the metabolic syndrome, impaired glucose tolerance (IGT), obesity and diabetes

Free fatty acids (FFA) are the form in which fatty acids are transported from their storage in adipose tissue to their sites of utilisation in liver and muscle. Fatty acids are stored in adipose tissue as triglycerides. Lipolysis results in release of FFA and glycerol into plasma, in response to stress, prolonged fasting or lack of insulin. Triglycerides are fatty acid esters of glycerol, usually a mixture of two or three fatty esters. Dietary fatty acids are absorbed mainly in form of chylomicrons which enter the systemic circulation via the intestinal lymphatic vessels and the thoracic duct. Triglyceride levels in plasma are determined by the secretion rate of very low density lipoproteins (VLDL) from the liver and by the elimination of VLDL-triglycerides from the circulation by the action of lipoprotein lipase (Thompson 1989).
Nearly all tissues have the capacity to synthesise cholesterol, but under normal conditions all newly synthesized cholesterol originates from the liver and distal part of the intestine.

All lipids, except FFA, are transported in plasma in the form of lipoproteins. Ultracentrifugation isolates six classes of lipoproteins from postprandial plasma. The classes are chylomicrons, VLDL, IDL, LDL, HDL and Lp(a). Apo B is a structural component of VLDL and LDL, and Apo A-I is a structural component of HDL (Thompson 1989).

In the metabolic syndrome, insulin resistance is thought to be the basic disturbance. The cardiovascular risk factors that make up the metabolic syndrome are obesity (especially of upper body type) dyslipidaemia with high triglyceride and low HDL-cholesterol levels, hypertension, and low fibrinolytic activity. Sometimes the syndrome also includes impaired glucose tolerance (IGT) (Reaven 1988). Obesity promotes the development of insulin resistance and weight loss can reverse the progress (Olefsky, Reaven et al. 1974).

Adipose tissue is now recognised as a highly metabolic and endocrine organ. Human glycogen stores are small, therefore triglycerides stored in adipose tissue represent the main long-term store for excess energy. The amount of triglycerides stored within adipocytes reflects the long-term balance between energy intake and energy expenditure (Frayn, Karpe et al. 2003).

Ageing and westernisation of developed and developing countries have led to a dramatic increase in the global prevalence of diabetes. About 25% of diabetics have an autoimmune form – type-I (beta-cell destruction), but the vast majority (60-70%) have type-II (with the metabolic syndrome) (Groop 2000). The WHO has recently revised and refined the criteria for diabetes mellitus and the metabolic syndrome (Alberti and Zimmet 1998).

Circadian rhythmicity in the human body

Most functions in the human body e.g. hormones, body temperature and lipids have a round-the-clock rhythm. A relation between endogenous, i.e. genetically controlled biological rhythms and environmental factors has been recognised for some decades, especially the fact that light is capable of determining the timing of circadian rhythms and can act as a synchroniser (Haus and Touitou 1992). The role that disturbed circadian rhythms play in the effects of
shift work is of great interest. In a recent review article about disease mechanisms in shift workers, the secretion pattern of the pineal gland was regarded as the best marker of the circadian rhythm (Knutsson and Bøggild 2000).

In the same article, the authors also stated that shift work can result in a phase shift of circadian rhythm relative to the day-night cycle, in internal desynchronisation of differential internal body rhythms, and in reduced rhythm amplitude. The extent to which repeated displacement of circadian rhythms contributes to more "stationary metabolic consequences" is highlighted in recently published articles that have demonstrated an altered metabolic response to equivalent test meals when comparing after phase shift, with before phase shift (Hampton, Morgan et al. 1996; Romon, LeFur et al. 1997; Morgan, Arendt et al. 1998; Ribeiro, Hampton et al. 1998; Lund, Arendt et al. 2001; Sopowski, Hampton et al. 2001).

In addition, metabolic effects of sleep deprivation have been seen, as the rate of glucose clearance after injection was nearly 40% slower in the sleep-debt condition than in the sleep recovery condition (Spiegel, Leproult et al. 1999).

Specific rhythmicity of biomarkers such as glucose, corresponding insulin secretion and lipids

Depending on the work schedule, two individuals may perceive the same time of day differently. Phase-shifts, phase-drift, and within-group desynchronisation are important to keep in mind when interpreting experimental or laboratory results (Haus and Touitou 1992). For example, allowing for the effects of circadian rhythm and sleep on the regulation of glucose levels and insulin secretion when analysing biomarkers such as glucose and insulin has not been considered until very recently (Van Cauter, Polonsky et al. 1997; Scheen and Van Cauter 1998). Human sleep is generally consolidated into a single seven to nine hour period, meaning that fragmented sleep is exceptional. An important metabolic consequence of this pattern of sleep is that humans fast for an extended period every day, generally overnight. In actual fact, glucose levels rise initially, but remain stable or fall only minimally during the night (Van Cauter, Polonsky et al. 1997). In a French study (Simon, Weibel et al. 2000) it was demonstrated that even regular night workers, i.e. those most likely to adjust their circadian system to the nocturnal pattern, only partially adapted their 24-hour rhythms of plasma glucose and insulin secretion.
rate (ISR). Evidence of a circadian rhythm of ISR independent of plasma glucose has been successfully demonstrated by euglycaemic clamp techniques (Boden, Ruiz et al. 1996). In earlier research, two other forms of pulsatile insulin secretion were found - insulin secreted in rapid pulsations every 10-14 minutes and slower circoral oscillations, recurring every 1-3 hours (Boden, Ruiz et al. 1996; Van Cauter, Polonsky et al. 1997; Polonsky, Sturis et al. 1998).

As regards variations in lipid levels, both diurnal and monthly intra-individual variability have been confirmed. In a Norwegian study, the mean coefficient of variation (CV) for diurnal biological variability was 2.4% for cholesterol, 3.5% for HDL-cholesterol and 29.5% for triglycerides. The corresponding monthly biological variabilities were 4.2%, 4.1% and 20.7% respectively (Wasenius, Stugarard et al. 1990). The issues of circadian variability are more complicated, as both biological variation and pre-analytical variation must be taken into account (Evans and Laker 1995). Rivera-Coll A et al showed, by collecting blood from 25 individuals every four hours over a 24-h period, that the cosinusoidal function best fits all the 150 experimental data for each lipid category. The percentage of the total daily variation that is attributable to the circadian rhythm was huge (Rivera-Col, Funtes-Arderiu et al. 1994). When measuring total cholesterol, overnight fasting is not necessary. However, overnight fasting strongly influences the measurement of triglycerides and HDL-cholesterol (Evans and Laker 1995).

Shift related dietary intake and energy expenditure in day and shift workers.

In a Swedish study it was concluded that two-shift and three-shift work have a negligible impact on total dietary quality or coffee/tea consumption, but that 3-shift workers redistribute their food intake - eating at night instead (Lennernaes, Hambraeus et al. 1995). A circadian redistribution of food intake and nocturnal eating might have negative metabolic consequences because of circadian rhythm factors (Lennernaes, Akerstedt et al. 1994). Another Swedish researcher recently demonstrated that in a test situation, there was no time-of-day effect in energy expenditure and heat release over a 24-hour period, and no total 24-hour difference between individuals who were night-eating or night-fasting. These results were obtained under special conditions when the test individuals kept a constant 24-h total
caloric intake over the whole test period (Holmback 2002). This does not support the hypothesis put forward by Romon et al (Romon, Edme et al. 1993) that circadian variation of diet-induced thermogenesis can promote weight gain in shift workers eating snacks at night.

PUBLISHED EPIDEMIOLOGICAL RESEARCH INTO METABOLIC RISK FACTORS IN SHIFT WORKERS

Impairment of metabolic biomarkers may be the result of one or more of the three suggested pathways by which shift work may predispose to CVD. These suggested pathways are i) mismatch of circadian rhythms, ii) behavioural changes e.g. diet, smoking, and iii) disturbed socio-temporal patterns e.g. stress (Knutsson and Bøggild 2000). These metabolic biomarkers may also be risk factors for other health problems. Some of these health effects have been discussed briefly above. However, I should like to discuss specific metabolic disturbances from an epidemiological perspective. The different risk factors are discussed according to the way they are linked together in research, and they are not ranked according to their significance for human health.

Triglycerides, Total cholesterol and HDL-cholesterol

Eleven studies of triglycerides in shift workers have been published in international journals. Two of these provided no information about sampling procedures (Bursey 1990; Costa, Betta et al. 1990), whereas nine studies provided this information (fasting state, clock time) (Thelle, Förde et al. 1976; Orth-Gomér 1983; De Backer, Kornitzer et al. 1987; Knutsson, Åkerstedt et al. 1988; Knutsson, Andersson et al. 1990; Romon, Nuttens et al. 1992; Lasfargues, Vol et al. 1996; Nakamura, Shimai et al. 1997; Nagaya, Yoshida et al. 2002). Six out of nine studies demonstrated increased concentrations of triglycerides in shift workers compared to day workers (Orth-Gomér 1983; Knutsson, Åkerstedt et al. 1988; Romon, Nuttens et al. 1992; Lasfargues, Vol et al. 1996; Nakamura, Shimai et al. 1997; Nagaya, Yoshida et al. 2002). In five of the studies fasting samples were taken in the morning (Orth-Gomér 1983; Romon 1992; Knutsson, Åkerstedt et al. 1988; Nakamura, Shimai et al. 1997; Nagaya, Yoshida et al. 2002), whereas in
the other studies information about fasting state and clock time was incomplete.


Only four studies have looked at HDL-cholesterol in shift workers. (De Backer, Kornitzer et al. 1987; Costa, Betta et al. 1990; Romon, Nuttens et al. 1992; Nagaya, Yoshida et al. 2002). Two of these reported no difference between shift- and day workers (Costa, Betta et al. 1990; Romon, Nuttens et al. 1992) whereas one study showed that the HDL-cholesterol was lower in shift workers (De Backer, Kornitzer et al. 1987).

**Fibrinolytic activity, fasting glucose, HBA1c, insulin, type-II diabetes, as isolated biomarkers or in combination**

The effect that shift work has on fibrinolytic parameters is rarely discussed (Peternel, Stegnar et al. 1990; Bøggild and Jeppesen 2001). The effects on glucose and diabetes are rarely debated in specialist magazines. However, two early studies have shown that type of day-work schedule affects glucose (Orth-Gomér 1983) and HBA1c (glycosylated haemoglobin) levels (Cesana, Panza et al. 1985).

Another recently published study showed that more ergonomic scheduling did improve HBA1c, markers of homeostasis and lipids (Bøggild and Jeppesen 2001). Koller (Koller 1983), has also suggested that endocrine and metabolic disorders are more prevalent in shift workers. In addition, two studies – one cross-sectional (Mikuni, Ohoshi et al. 1983) and the other longitudinal (Kawachi, Colditz et al. 1995) - showed that diabetes was more common among shift workers.
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than day workers. Furthermore, a recent Japanese cohort study found that overtime was the strongest predictor for diabetes and shift work exposure was also a risk factor of substance (Kawakami, Araki et al. 1999).

Measurements of obesity and the metabolic syndrome

Previous research into obesity in shift workers has yielded contradictory results. Seven studies showed no difference in anthropometric parameters in shift workers compared with day workers (Orth-Gomér 1983; Cesana, Panza et al. 1985; De Backer, Kornitzer et al. 1987; Knutsson 1989; Bursey 1990; Costa, Betta et al. 1990; Romon, Nuttens et al. 1992). However, other studies have shown obesity to be more common in shift workers. These studies measured obesity in kilograms (Bøggild, Suadicani et al. 1999), BMI (Kawachi, Colditz et al. 1995; Niedhammer, Lert et al. 1996; Kivimaeki, Kuisma et al. 2001; Parkes 2002), waist/hip-ratio (Nakamura, Shimai et al. 1997), or both high BMI and waist/hip-ratio combined (Rosmonds, Lapidus et al. 1996; van Amelsvoort, Schouten et al. 1999). Only one study has aggregated several metabolic risk factors such as hypertension, hyperglycaemia, hypertriglyceridaemia and low HDL-cholesterol (Nagaya, Yoshida et al. 2002). This study concluded that working shifts was associated with changes in metabolic risk factors that could be related to insulin resistance in workers aged less than 50 years.

Hypertension and cardiac rhythm

Most earlier studies on shift workers have not found any difference in blood pressure between shift- and day workers (Bøggild and Knutsson 1999). However, when ambulatory blood pressure is measured and the circadian influence is taken into consideration, a longer plateau of high blood pressure was described during the night in four of the studies (Chau, Mallion et al. 1989; Goto, Yokoyama et al. 1994; Yamasaki, Schwartz et al. 1998; Ohira, Tanigawa et al. 2000). These findings are not consistent, though. In three other studies no differences were found between shift workers and day workers (Sundberg, Kohvakka et al. 1988; Baumgart, Walger et al. 1989; Motohashi, Higuchi et al. 1998). One Japanese cohort study (Morikawa, Nakagawa et al. 1999), demonstrated an association
between three-shift patterns and the onset of hypertension. Another Japanese cohort study (Murata, Yano et al. 1999) showed no such effects but did show a prolongation of the heart-rate-adjusted QT-interval (QTc) in shift workers. A prolongation of the QT-interval may represent a serious threat to health as it may be associated with a risk of serious cardiac arrhythmia including sudden death.

**Homocysteine**

Recently, increased levels of plasma homocysteine were found in male shift-working busdrivers in Brazil. No previous studies have looked at plasma homocysteine levels in shift workers. There is considerable evidence that hyperhomocysteinaemia could be a risk factor for cardio- and cerebrovascular disease in shift workers, independent of all other known metabolic risk factors (Martins, DÁlmeida et al. 2003).

**MECHANISMS OF SELECTION**

**Selection in the general population**

The healthy worker survivor effect is well known. This refers to the continuous selection process whereby those individuals who remain employed tend to be healthier than those who leave employment. The healthy hire effect is also well recognised. This is the bias introduced by the initial selection process in which healthy individuals are more likely to seek and gain employment than those who are less healthy. The time-since–hire, i.e. the non-comparability of recent and earlier hires, is a third source of bias. All these effects in combination are termed the "healthy worker effect" (Arrighi and Hertz Picciotto 1994).

This phenomenon makes it difficult to show excesses of occupationally related diseases with epidemiological studies.

For example, differences in disease prevalence in specific groups of workers as compared with the national population may reflect important socio-economic influences or may be distorted by the selection of healthy persons for employment, or both. Low socio-economic status, for example, is associated with unemployment as well as with poor health (Wilcosky and Wing 1987).
It is fairly obvious that employment is accompanied by substantial life changes, e.g. economic status may improve, medical care may be more accessible, and substantial changes in lifestyle may occur (Wen and Tsai 1982).

In the USA, workers in plants with more than 500 employees are four times more likely to undergo a pre-employment physical examination than in plants that employ fewer than 250, and therefore health selection is more likely in large plants. Once hired, workers in large plants have much greater access to services that protect their health (Wilcosky and Wing 1987).

However, a number of strategies for minimising the healthy worker effect in research have been suggested. Of these, ‘use of external work comparison groups’ or ‘use of internal comparison groups’, are the most methodologically plausible. Individuals working together in the same workforce are likely to have gone through the same employment selection process, which makes internal comparisons one of the most effective ways of reducing the “healthy worker effect” when making statistical comparisons (direct age standardisation) (Li and Sung 1999).

Selection in day and shift work

In general, we do not know whether a more specific selection effect occurs when a new job applicant is selected for shift work as opposed to day work. A survey carried out at a Swedish plant showed there were no major differences in biochemical and anthropometric data between applicants for day and shift work. The only difference may have been a self-selection by individuals with specific sleep behaviours that may have made them particularly suitable for working odd hours (Knutsson and Akerstedt 1992). According to other published studies, the attitudes and feelings of those employees that opt voluntarily for shift work enables them to adjust more easily to shift work (Barton 1994). One previous study has reported an association between hormonal levels and satisfaction. Dissatisfied shift workers had lower morning testosterone levels than satisfied shift workers (Axelsson, Åkerstedt et al. 2003). There are no reliable methods or tools that can identify in advance those individuals that have a greater capacity to cope with shift work, or those that are potentially unfit or unable to cope with shift work and who should be encouraged to avoid it (Härma 1993; Nachreiner 1998).
A further selection process can be seen during shift work. Inability to cope with this pattern of work may appear during the first year, mainly in the form of sleep problems, disruption of circadian rhythm and social disruption (Härmä 1993). Perhaps as many as 25% of all shift workers can be identified as "non-shift adapters" when exposed to several consecutive night shifts, as demonstrated by a non-adaptive cortisol rhythm, a reduction of sleep duration and a lower "satisfaction with life" score (Hennig, Kieferdorf et al. 1998).

Later on, gastrointestinal and cardiovascular disturbances occur (Harrington 1994; Costa 1996) and these diseases are more prevalent in shift work drop-outs (Koller 1983).

In fact, the incidence of most human diseases increases with age, and this may represent selection pressure out of shift work. It is worth noting that most studies are cross-sectional, and their results may therefore be affected by a "healthy worker effect" bias (Costa 2003).
THE AIMS OF THE THESIS

The main aim was to explore metabolic effects in relation to shift work

The specific aims of the four studies were:

- To monitor the effects of intake of ordinary meals at different times of the night on serum glucose, serum insulin and serum triglycerides. (Paper 1)

- To investigate in two different shift-exposed populations whether shift work is associated with metabolic risk factors for CHD and type-II diabetes. (Paper 2 and Paper 3)

- To compare shift workers with day workers with respect to total mortality and cause specific mortality for diabetes, coronary heart disease and ischaemic stroke. (Paper 4)

The committees of ethics, Umeå University, Sahlgrenska University Hospital and Karolinska Institute approved the studies included in this thesis.
STUDY POPULATIONS AND METHODS

INTERVENTION STUDY (PAPER I)

Eleven female nurses, aged 33-53, from the Department of Clinical Medicine at the University Hospital of Umeå were included. All nurses were healthy and had no signs of diabetes or any other metabolic disease. The work schedule included 7 nights during a 3-week period, and working hours were between 21:00-07:00. The intervention was carried out during the second working week, and for three days before the start of the study the subjects had to comply with a regular schedule of standardised meals. The test meals were ingested at different times during 3 separate night shifts - at 19:30, 23:30 or 03:30. Blood was sampled at baseline and postprandially at 30, 60, 90, 120, 180 and 240 minutes. Biochemical analysis of serum glucose, insulin and triglycerides was performed.

A wrist actograph was used to monitor sleep/wake behaviour. Specific information about measurement procedures and calculations is given under "Methods" in Paper I.

CROSS-SECTIONAL STUDY (PAPER II)

Between 1992 and 1997 a total of approximately 40 000 men and women took part in the Västerbotten intervention programme (VIP), which was aimed at preventing cardiovascular disease and diabetes. After exclusions, 27 485 subjects in permanent work, temporary work or self-employment at the time of the health examination remained in the study. Shift workers were defined as answering "yes" to the question: "do you work shifts or weekends?" Through cross-tabulation of the variables 'occupations' coded according to the Nordic Classification of Occupations 1983, and 'shift work', a validation of the classification of shift workers was obtained. (Table 1)

For methods used in blood sampling, laboratory tests, oral glucose tolerance tests (OGTT), anthropometry and blood pressure measurement, as well as definitions used for the classification of socio-economic status, diabetes, hypertension, impaired glucose tolerance (IGT), fasting plasma glucose and cut-off points see under "Methods" in Paper II.
Table 1. Validation of occupations coded accorded to the Nordic Classifications of Occupations 1983, in the VIP study.

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Number of Men shift v day workers</th>
<th>% Shift workers¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper and pulp workers</td>
<td>39/45</td>
<td>87</td>
</tr>
<tr>
<td>Miners</td>
<td>48/58</td>
<td>83</td>
</tr>
<tr>
<td>Bus and taxi drivers</td>
<td>192/275</td>
<td>70</td>
</tr>
<tr>
<td>Truck drivers</td>
<td>219/361</td>
<td>61</td>
</tr>
<tr>
<td>Saw mill workers</td>
<td>62/166</td>
<td>37</td>
</tr>
<tr>
<td>Engineers</td>
<td>65/983</td>
<td>7</td>
</tr>
<tr>
<td>Teachers</td>
<td>21/437</td>
<td>5</td>
</tr>
<tr>
<td>Carpenters</td>
<td>7/176</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Number of Women shift v day workers</th>
<th>% Shift workers¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assistant nurses</td>
<td>851/984</td>
<td>86</td>
</tr>
<tr>
<td>Nurses</td>
<td>303/469</td>
<td>65</td>
</tr>
<tr>
<td>Shop assistants</td>
<td>250/575</td>
<td>43</td>
</tr>
<tr>
<td>Kitchen staff and cooks</td>
<td>70/208</td>
<td>34</td>
</tr>
<tr>
<td>Children’s nurses</td>
<td>84/645</td>
<td>13</td>
</tr>
<tr>
<td>Teachers</td>
<td>37/700</td>
<td>5</td>
</tr>
<tr>
<td>Secretaries</td>
<td>29/443</td>
<td>3</td>
</tr>
<tr>
<td>Dental nurses</td>
<td>4/136</td>
<td>3</td>
</tr>
</tbody>
</table>

¹ Prevalence of shift workers in a listed number of occupations in the study group

CROSS-SECTIONAL STUDY (PAPER III)

The purpose of the Work, Lipids and Fibrinogen (WOLF) study, was to investigate the relationship between occupational, including psychosocial, conditions and cardiovascular risk factors. From this study, a subgroup of men employed in two pulp and paper manufacturing plants in the north of Sweden, with complete laboratory data, were selected. The data collection from these two plants took place between September 1996 and December 1997. The exposures to day and shift work were obtained from the WOLF questionnaire. The analysis included 665 day workers and 659 three-
shift workers. For methods used in data collection, blood sampling, laboratory procedures, anthropometry and blood pressure measurement, classification of socio-economic status, physical activity, current smoking, job strain, low social support and cut-off points see under "Methods" in Paper III.

**COHORT STUDY (PAPER IV)**

The study population comprised male workers at two pulp and paper manufacturing plants run by the same company in the north of Sweden. The study population was restricted to blue-collar workers registered in company files, who had been employed for at least six months between January 1, 1940 and December 31, 1998. Information was obtained about shift exposure from first date of employment for each individual in the cohort. Using job title in conjunction with the specific workplace it was possible to classify each individual in terms of exposure to day work and different categories of shift work. After some exclusions (described in Paper IV), the remaining subjects, consisting of 2,354 shift workers and 3,088 day workers, were studied with regard to total and cause specific mortality from CHD, diabetes or ischaemic stroke from January 1, 1952 to December 31, 2001.

(The defined ranges of diagnostic codes are described in the appendix to Paper IV)

**STATISTICAL METHODS**

**Paper I**

The postprandial responses were estimated as the total area under curve (AUC) calculated using the trapezoidal rule. Repeated measures ANOVA (one way ANOVA) were used to compare values taken at three time points.

**Paper II and Paper III**

Pearson’s chi-square test and Student’s t-test were used to compare proportions and continuous variables respectively. Multiple logistic regression was used for multivariate analysis.
Subjects and methods

In Paper III linear regression was used for test of interaction with continuous variables, and in Paper II age adjustment was accomplished with direct standardisation.

All data analysis in Paper I, II and III was carried out in SPSS, version 10.0

Paper IV

Mortality rates were expressed as the number of deaths (total or according to diagnosis) divided by the total time at risk for the group in question. Subjects could contribute to the time at risk within different shift exposure categories. Thus, a subject contributed to the time at risk within a specific shift exposure category until he fulfilled the requirements for the next shift exposure category.

The mortality among subjects in different shift exposure categories was compared with the corresponding mortality among day workers by calculating a relative rate together with a 95% confidence interval. In order to take differences in age distributions into account, standardised relative rates (SRR) were calculated based on weights derived from the unexposed group. The standardisation was based on five-year age groups. Ninety-five percent confidence intervals were computed assuming a Poisson distribution (Ahlbom 1993). Two analyses were carried out - the first on the full material and the second on occupationally active individuals. In the first analysis, the length of follow-up was as long as possible, i.e. without restrictions in age or employment. In the second analysis, the length of follow-up was restricted to end at age 68. (Workers usually retire at 65 years of age in Sweden.) For subjects who left their employment during the study period, follow-up was terminated at a maximum of four years after the end of employment. Trend analysis in order to assess the pattern of effects over exposure categories (years of shift work) was carried out using linear regression modelling (Rothman 1986).
Basal glucose values were similar at 19:30, 23:30 and 03:30. The peak values differed with the highest value observed after food intake at 23:30 (Figure 1). The postprandial glucose response was higher after meal ingestion at 23:30, but the differences in AUC did not reach statistical significance.

Figure 1. Postprandial glucose response to a test meal ingested at three different times during night work.

Basal insulin levels were different at baseline 19:30, 23:30 and 03:30. The highest value was observed at 23:30 and the lowest at 03:30. The postprandial insulin responses were highest after meal ingestion at 23:30, and lowest after 03:30. (Figure 2). There were no significant differences in postprandial triglyceride curves.
Results

Figure 2. Postprandial insulin response to a test meal ingested at three different times during night work.

Table 2 Prevalences of metabolic risk factors in the VIP-study.

<table>
<thead>
<tr>
<th>Age group</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides &gt;1.7 mmol/L (%)</td>
<td>8.7</td>
<td>8.6</td>
<td>13.7</td>
<td>9.6***</td>
</tr>
<tr>
<td>Low HDL-cholesterol (%)(^1)</td>
<td>18.3</td>
<td>8.6***</td>
<td>16.4</td>
<td>13.5</td>
</tr>
<tr>
<td>Hypertension (%)(^2)</td>
<td>2.5</td>
<td>3.6</td>
<td>9.1</td>
<td>8.0</td>
</tr>
<tr>
<td>BMI &gt;=30 (%)</td>
<td>9.1</td>
<td>6.6*</td>
<td>10.8</td>
<td>7.2***</td>
</tr>
<tr>
<td>Diabetes (%)(^3)</td>
<td>1.3</td>
<td>1.5</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Men:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides &gt;1.7 (%)</td>
<td>22.4</td>
<td>20.1</td>
<td>31.5</td>
<td>28.5(*</td>
</tr>
<tr>
<td>Low HDL-cholesterol (%)(^1)</td>
<td>26.7</td>
<td>17.9*</td>
<td>20.1</td>
<td>19.8</td>
</tr>
<tr>
<td>Hypertension (%)(^2)</td>
<td>7.3</td>
<td>5.7</td>
<td>15.5</td>
<td>12.3***</td>
</tr>
<tr>
<td>BMI &gt;=30 (%)</td>
<td>10.4</td>
<td>4.9***</td>
<td>12.1</td>
<td>7.9***</td>
</tr>
<tr>
<td>Diabetes (%)(^3)</td>
<td>0.9</td>
<td>1.1</td>
<td>2.6</td>
<td>2.1</td>
</tr>
</tbody>
</table>

P-values < 0.1(*), < 0.05*, < 0.01**, < 0.001***

1Women <1.0 , Men <0.9 mmol/l.
2Systolic BP > 160 mmHg or diastolic BP > 90 mmHg or using antihypertensive drugs.
3Fasting P-glucose >=7.0 or 2 hours level >= 12.2 mmol/l or answering yes to having diabetes.
Results

Prevalences of main metabolic risk factors among day and shift workers in different age groups for men and women in the VIP-study are presented in table 2.

Clustering of metabolic risk variables with combinations of obesity, raised triglyceride concentrations and hypertension was more common in shift workers than in day workers (Figure 3).

Figure 3.
Reanalysing the data in the VIP-cohort has shown that among those with normal triglycerides, obesity was significantly more common in shift workers than day workers in nearly all strata (Table 3 and table 4). This was seen in both sexes. However, in individuals with elevated triglycerides (>1.7 mmol/l) there were no difference with regard to obesity between shift and day workers (data not shown).

Table 3. Prevalence of obesity among female (%) in the VIP study.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Subjects with normal triglycerides (&lt;=1.7 mmol/L)</th>
<th>Subjects with normal HDL-cholesterol (&gt;=0.9 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Shift</td>
</tr>
<tr>
<td>30</td>
<td>5.3</td>
<td>7.5</td>
</tr>
<tr>
<td>40</td>
<td>5.9</td>
<td>7.7</td>
</tr>
<tr>
<td>50</td>
<td>9.0</td>
<td>12.4</td>
</tr>
<tr>
<td>60</td>
<td>11.9</td>
<td>15.2</td>
</tr>
</tbody>
</table>

* 95% Confidence interval

Table 4. Prevalence of obesity among male (%) in the VIP study.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Subjects with normal triglycerides (&lt;=1.7 mmol/L)</th>
<th>Subjects with normal HDL-cholesterol (&gt;=0.9 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Shift</td>
</tr>
<tr>
<td>30</td>
<td>3.5</td>
<td>7.4</td>
</tr>
<tr>
<td>40</td>
<td>5.8</td>
<td>8.3</td>
</tr>
<tr>
<td>50</td>
<td>6.5</td>
<td>8.8</td>
</tr>
<tr>
<td>60</td>
<td>9.0</td>
<td>13.7</td>
</tr>
</tbody>
</table>

* 95% Confidence interval

After adjustment for age and socio-economic status, the elevated odds ratio for increased BMI and raised triglycerides persisted in both men and women (Table 5).
Table 5. Relative risk of obesity, low HDL cholesterol and high triglycerides associated with shift work (results of multiple logistic regression).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative risk of high BMI (obesity)</th>
<th>Relative risk of low HDL cholesterol</th>
<th>Relative risk of high triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>OR*</td>
<td>95% CI</td>
</tr>
<tr>
<td>Shift work</td>
<td>1.41</td>
<td>1.26 to 1.57</td>
<td>1.44</td>
</tr>
<tr>
<td>Shift work†</td>
<td>1.47</td>
<td>1.31 to 1.63</td>
<td>1.52</td>
</tr>
<tr>
<td>Shift work§</td>
<td>1.39</td>
<td>1.25 to 1.55</td>
<td>1.44</td>
</tr>
</tbody>
</table>

*Odds ratio obtained through multiple logistic regression.
†Crude odds ratio.
§Odds ratio adjusted for age.
$Odds ratio adjusted for age and socioeconomic group.
Results

PAPER III

In the WOLF-study the prevalences of the metabolic characteristics of high triglycerides, low HDL-cholesterol and increased waist/hip ratio were significantly higher in male shift workers compared to day workers (Table 6).

Table 6. Prevalences of metabolic risk factors among male day and shiftworkers in the WOLF study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dayworker</th>
<th></th>
<th>Shiftworker</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides&gt;=1.7mmol/L</td>
<td>25.1</td>
<td>167</td>
<td>32.5</td>
<td>214</td>
<td>0.003</td>
</tr>
<tr>
<td>HDL-cholesterol&lt;0.9mmol/L</td>
<td>3.9</td>
<td>26</td>
<td>7.6</td>
<td>50</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertension1</td>
<td>21.1</td>
<td>140</td>
<td>16.9</td>
<td>111</td>
<td>0.052</td>
</tr>
<tr>
<td>BMI&gt;=30</td>
<td>14.3</td>
<td>95</td>
<td>15.0</td>
<td>99</td>
<td>0.705</td>
</tr>
<tr>
<td>Waist hip ratio&gt;0.9</td>
<td>62.9</td>
<td>416</td>
<td>69.5</td>
<td>457</td>
<td>0.012</td>
</tr>
<tr>
<td>Hyperglycaemia2</td>
<td>2.0</td>
<td>13</td>
<td>2.0</td>
<td>13</td>
<td>0.981</td>
</tr>
<tr>
<td>HBA1c&gt;5.3%</td>
<td>10.5</td>
<td>70</td>
<td>8.1</td>
<td>53</td>
<td>0.124</td>
</tr>
<tr>
<td>Fasting insulin&gt;13mikromol/L</td>
<td>10.3</td>
<td>67</td>
<td>9.1</td>
<td>58</td>
<td>0.489</td>
</tr>
<tr>
<td>Total cholesterol &gt;6.4mmol/L</td>
<td>28.1</td>
<td>187</td>
<td>19.0</td>
<td>125</td>
<td>0.000</td>
</tr>
</tbody>
</table>

1Systolic BP>160mmHg, diastolic BP>90mmHg or using antihypertensive drugs
2Fasting serum glucose >=7.0mmol/L.

When adjusting for age, socio-economic group, physical activity, current smoking, low social support and job strain, shift work was still a significant predictor for high triglycerides and low HDL-cholesterol levels (Table 7).
Table 7. Odds ratio of low HDL-cholesterol, obesity and high triglycerides associated with shiftwork. Results of multiple logistic regression.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Low HDL-cholesterol</th>
<th>High triglycerides</th>
<th>Abdominal obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR*</td>
<td>95% CI**</td>
<td>OR*</td>
</tr>
<tr>
<td>Shiftwork(^1)</td>
<td>2.02</td>
<td>1.24-3.28</td>
<td>1.43</td>
</tr>
<tr>
<td>Shiftwork(^2)</td>
<td>1.85</td>
<td>1.13-3.07</td>
<td>1.41</td>
</tr>
<tr>
<td>Shiftwork(^3)</td>
<td>1.81</td>
<td>1.10-2.99</td>
<td>1.39</td>
</tr>
<tr>
<td>Shiftwork(^4)</td>
<td>1.79</td>
<td>1.09-2.96</td>
<td>1.39</td>
</tr>
<tr>
<td>Shiftwork(^5)</td>
<td>1.83</td>
<td>1.10-3.06</td>
<td>1.39</td>
</tr>
<tr>
<td>Shiftwork(^6)</td>
<td>2.03</td>
<td>1.18-3.48</td>
<td>1.40</td>
</tr>
</tbody>
</table>

\(^*\) Odds ratio obtained through multiple logistic regression.
\(^**\) CI=Confidence Interval.
\(^1\) Crude odds ratio.
\(^2\) Odds ratio adjusted for age.
\(^3\) Odds ratio adjusted for age and socioeconomic group.
\(^4\) Odds ratio adjusted for age, socioeconomic group, physical activity and current smoking.
\(^5\) Odds ratio adjusted for age, socioeconomic group, physical activity, current smoking, and low social support.
\(^6\) Odds ratio adjusted for age, socioeconomic group, physical activity, current smoking, low social support and job strain.

In order to assess differences between ages, a split into young (\(<=50\) years) and old (\(>50\) years) workers showed after adjustment for age, socio-economic status, physical activity, and smoking that shift work was a predictor for obesity only in young workers (OR: 1.39, 95%CI: 1.05-1.85 vs. OR: 1.1, 95%CI: 0.66-1.86).
PAPER IV

The rate of death due to any cause (total mortality), was no higher in shift workers than in day workers. (SRR= 1.02, 95% Confidence Interval (95%CI) 0.93-1.11) (Table 8).

Mortality due to coronary heart disease (CHD) was 11% higher in shift workers than in day workers. (SRR 1.11, 95%CI 0.95-1.30). The risk was most pronounced among those with 30 years or more of shift work experience (SRR= 1.24, 95%CI 1.04-1.49). Higher duration of shift work was associated with an increased risk of coronary heart disease (b=16.4x10^{-5},95%CI 13.2x10^{-5}-19.7x10^{-5}).

When all shift workers were compared with day workers, a difference in mortality due to ischaemic stroke was observed (SRR=1.56, 95%CI 0.98-2.51). The highest relative rate ratio was observed for those having the shortest experience of shift work (less than five years) with a SRR of 4.57 (95%CI 1.58-13.21), although this was based on only four exposed cases. The SRR for mortality due to diabetes associated with shift work was 1.24, (95%CI 0.91-1.70). The SRR for diabetes was 1.54 (95%CI 0.93-2.57) in those that had been employed as a shift worker for 20-29 years, and in workers with 30 or more years' experience of shift work the corresponding figure was 1.22 (95%CI 0.84-1.79). The risk of dying with diabetes as an underlying contributory cause increased with increasing number of shift years (b=4.14x10^{-5}, 95%CI 2.46x10^{-5} –5.81x10^{-5}).

Discontinuing follow-up at a maximum of 68 years of age (or at a maximum four years after termination of employment; i.e. an age closer to exposure) reduced the number of exposed cases and widened confidence intervals. With the exception of diabetes, all results were similar to those obtained from analysis of the full material. For diabetes, the overall SRR was 2.29 (95%CI 0.97-5.40). Mortality due to diabetes increased with increasing exposure to shift work. The SRR in this group rose from 1.41 (95%CI 0.18-11.36) after 10-19 years, rising to 1.92 (95%CI 0.50-7.32) at 20-29 years, and to 2.35 (95%CI 1.15-7.08) after 30 years or more of shift work.
Table 8. SRR for total mortality, cardiovascular disease, stroke and diabetes among shift workers compared to day workers.

<table>
<thead>
<tr>
<th>Years of shiftwork</th>
<th>Total mortality</th>
<th></th>
<th></th>
<th></th>
<th>Coronary heart disease</th>
<th></th>
<th></th>
<th></th>
<th>Ischaemic Stroke</th>
<th></th>
<th></th>
<th></th>
<th>Diabetes</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of exp cases</td>
<td>Ratio*</td>
<td>CI**</td>
<td>No of exp cases</td>
<td>Ratio*</td>
<td>CI**</td>
<td>No of exp cases</td>
<td>Ratio*</td>
<td>CI**</td>
<td>No of exp cases</td>
<td>Ratio*</td>
<td>CI**</td>
<td>No of exp cases</td>
<td>Ratio*</td>
<td>CI**</td>
<td></td>
</tr>
<tr>
<td>Shift&lt; 5 years</td>
<td>46</td>
<td>0.99</td>
<td>0.65-1.50</td>
<td>10</td>
<td>0.85</td>
<td>0.30-2.38</td>
<td>4</td>
<td>4.57</td>
<td>1.58-13.2</td>
<td>3</td>
<td>0.57</td>
<td>0.17-1.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shift&gt;=5 - &lt;10</td>
<td>40</td>
<td>0.94</td>
<td>0.65-1.36</td>
<td>14</td>
<td>0.97</td>
<td>0.56-1.67</td>
<td>1</td>
<td>0.54</td>
<td>0.07-3.97</td>
<td>3</td>
<td>0.99</td>
<td>0.31-3.22</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Shift&gt;=10 - &lt;20</td>
<td>106</td>
<td>0.93</td>
<td>0.76-1.14</td>
<td>34</td>
<td>0.83</td>
<td>0.58-1.19</td>
<td>5</td>
<td>1.76</td>
<td>0.68-4.57</td>
<td>10</td>
<td>1.09</td>
<td>0.56-2.10</td>
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<td></td>
</tr>
<tr>
<td>Shift&gt;=20 - &lt;30</td>
<td>168</td>
<td>1.06</td>
<td>0.90-1.25</td>
<td>54</td>
<td>1.02</td>
<td>0.77-1.36</td>
<td>5</td>
<td>1.08</td>
<td>0.42-2.78</td>
<td>18</td>
<td>1.54</td>
<td>0.93-2.57</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shift&gt;=30</td>
<td>400</td>
<td>0.98</td>
<td>0.88-1.10</td>
<td>175</td>
<td>1.24</td>
<td>1.04-1.49</td>
<td>20</td>
<td>1.51</td>
<td>0.87-2.63</td>
<td>39</td>
<td>1.22</td>
<td>0.84-1.79</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All shift vs day</td>
<td>760</td>
<td>1.02</td>
<td>0.93-1.11</td>
<td>287</td>
<td>1.11</td>
<td>0.95-1.30</td>
<td>35</td>
<td>1.56</td>
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<td>73</td>
<td>1.24</td>
<td>0.91-1.70</td>
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</tr>
</tbody>
</table>

* All rates are age adjusted
** 95% Confidence interval
DISCUSSION

The main metabolic results in all four studies in this thesis suggest that exposure to shift work promotes the development of risk factors and associated outcomes, figure 4.

The bold text in figure 4 illustrates the outcomes, where specific new results or interpretations of results from all articles in this thesis are presented.
Obesity

Obesity is one of the major registered outcomes in two of the articles presented in this thesis. Human adipose tissue is nowadays recognised as a highly metabolic and endocrine organ (Frayn, Karpe et al. 2003). When comparisons between shift workers and day workers were made in the present cross-sectional studies, obesity was measured either as an increase in BMI or an increase in waist/hip ratio or both. It is important to bear in mind that fluctuations in obesity occur at a much slower pace than fluctuation in individual blood lipids.

Although these studies are cross-sectional in character, substantial bias is unlikely because selective transfer of obese workers from day work to shift work is unlikely.

Furthermore, as shown by reanalysis of the VIP data, individuals with normal triglycerides suffer from obesity significantly more often when working shifts than when working days. This is shown in nearly all groups in all age strata in both men and women. When the same analyses were done on individuals with normal HDL-cholesterol levels, obesity was no commoner in shift workers than day workers. This is plausible because normal HDL-cholesterol is associated with normal triglycerides, and low HDL-cholesterol occurs in association with high triglyceride concentration. Therefore, HDL-cholesterol is generally inversely correlated with body weight (Thompson 1989).

It seems that, although the design is cross-sectional, the results could be interpreted as showing a causal link between obesity and shift work, meaning that obesity is more common among shift workers compared to day workers and this precedes any disturbances of lipid concentrations. Likewise, in those subjects with established high triglycerides, obesity is commoner but is equally distributed between the groups i.e. between day and shift workers, and between men and women. This assumption is supported in particular by the WOLF-study, where shift work was a stronger predictor for obesity among young shift workers (age<=50 years), than it was among older shift workers (age>50years).

Increased anthropometric measures among shift workers compared to day workers in the two cross-sectional studies in this thesis concur
Discussion

with a number of recent shift work studies (Kawachi, Colditz et al. 1995; Niedhammer, Lert et al. 1996; Rosmonds, Lapidus et al. 1996; Nakamura, Shimai et al. 1997; van Amelsvoort, Schouten et al. 1999; Geliebter, Gluck et al. 2000; Kivimaeki, Kuisma et al. 2001; Parkes 2002; Al-Asi 2003; Di Lorenzo, De Pergola et al. 2003). Earlier studies often showed no difference between the exposure groups. This discrepancy could be explained by the possibility that the designs of the more recent studies are more rigorous. Nevertheless, it cannot be denied that a nearly exponential rise in obesity has been witnessed over the past decade in the western societies with a growing 24/7-economy, and this unfavourable development could quite plausibly be the result, at least in part, of shift work.

Free fatty acids (FFA)

Obesity is shown to be more common among shift workers in the two cross-sectional studies. The increased lipolysis seen in obesity raises blood FFA concentrations. The turnover of FFA in blood is normally extremely rapid (Thompson 1989), and in normal non-obese individuals, fatty meal intake does not have an impact on glucose metabolism. However, in obesity or type-II diabetes the elevation of FFA is more or less chronic, and this eventually leads to a failure to stimulate insulin secretion (Boden 1997).

In addition, FFA levels show diurnal variation - fasting FFA concentrations being higher in the evenings than in the mornings, irrespective of eating and exercise. Perhaps the relatively elevated FFA levels in the evenings are the cause and not the consequence of increased insulin resistance at this time of day (Morgan, Aspostolakou et al. 1999).

Altered glucose tolerance and altered insulin response

In the intervention study involving nurses in their normal night shift duties, the highest peak value for glucose after food intake was observed at 23:30. The postprandial glucose response was also higher after meal ingestion at 23:30. A more precise measurement of the internal biological rhythms of the participants does not exist in this study, but their schedule would suggest that they are not phase-shift adjusted. The meal responses with higher blood glucose concentration in the late evenings are in agreement with several other studies (Van

The highest postprandial insulin response was observed at 23:30 and the lowest responses at 03:30. The differences in AUCs were also statistically significant. These findings are also in agreement with earlier intervention studies (Van Cauter, Shapiro et al. 1992; Hampton, Morgan et al. 1996; Morgan, Arendt et al. 1998; Lund, Arendt et al. 2001). Diurnal variations in insulin sensitivity with better insulin sensitivity in the mornings has been standard knowledge for more than thirty years (Gibson and Jarrett 1972).

To draw conclusions, however, about glucose and insulin data from epidemiological studies is more difficult. These studies only provide a single blood sample from each individual at only one occasion. When one considers that even more subtle circadian or ultradian glucose and insulin oscillations exist in regular night workers (Simon, Weibel et al. 2000), and that these fluctuations are hard to measure in normal working life, one single measurement of glucose and insulin, albeit fasting, is difficult to interpret. After all, in the VIP and WOLF study no differences in hyperglycaemia (glucose>=7.0 mmol/l) prevalence was seen between shift and the day workers. A difference in fasting insulin was seen in the WOLF-study, where day workers showed a higher value than shift workers. This result was not expected and was difficult to interpret, but was assumed to be influenced by the internal circadian rhythm of insulin and may also have depended on the fact that blood was taken on average 2 h later among day workers (Boden, Ruiz et al. 1996).

Metabolic syndrome

Recently the metabolic syndrome was defined as a disturbance in the glucose-insulin axis, (type-II diabetes, impaired glucose tolerance or insulin resistance) in combination with two of the following criteria; high triglycerides or low HDL-cholesterol, increased blood pressure, central obesity or BMI>=30 and microalbuminuria (Alberti and Zimmet 1998; Groop 2000).

In none of the studies was it possible to obtain a complete set of laboratory tests that would fulfil the criteria for the metabolic syndrome. In the VIP study a method was chosen to illustrate how the metabolic factors of obesity, hypertension and high triglycerides tend to cluster in shift workers. In the WOLF study, prevalences of
triglycerides, low HDL-cholesterol, waist/hip ratio or BMI>=30, hypertension or fasting insulin > 13 mU/l were used, and some of them turned out as risk factors after several adjustments. (The reason why 13 mU/l was chosen when dichotomising the insulin variable can be found in a Finnish study (Laakso 1993) which showed that incidence of insulin resistance was 75% or more in the most insulin resistant tertile. This was independent of whether they were normal glucose tolerant (NGT), impaired glucose tolerant (IGT) or had non-insulin dependent diabetes mellitus (NIDDM)).

Only one other study (Nagaya, Yoshida et al. 2002) with a similar design, has compared a combination of several metabolic risk factors in shift workers vs. day workers. In this Japanese study they used a combination of laboratory tests that was somewhat different to that used in the VIP-study. They also found a significantly higher incidence in younger shift workers (< 50 years) of insulin resistance markers such as high triglycerides, hypertension, hyperglycaemia but not of low HDL-cholesterol. Adjustments were made for BMI (quartiles), occupation, drinking, smoking, exercise and lifestyle.

Altered triglycerides and HDL-cholesterol

Elevated triglycerides and low HDL-concentrations are the major lipid disturbances found in the two cross-sectional studies. These results were very stable in both the VIP-study when controlled for age and socio-economic factors and in the WOLF-study even when adjusted for age, socio-economic factors, physical activity, current smoking, low social support and job strain.

In the nurse intervention study no significant differences in triglycerides were seen in relation to meal times. This is in contrast to elevated triglyceride responses immediately after the phase shift shown by Ribeiro et al (Ribeiro, Hampton et al. 1998) and delayed or prolonged serum triglyceride response during night work as reported by two other authors (Hampton, Morgan et al. 1996; Lund, Arendt et al. 2001).

Normally, triglyceride levels remain elevated for several hours after ingestion of a fatty meal but all chylomicron triglycerides are normally cleared within 12 hours. Thus, measurement of plasma levels in the fasting state reflects the amount of endogenous triglyceride in the circulation (Thompson 1989). Mean total cholesterol concentrations do not change postprandially, but variations in both LDL-cholesterol
and HDL-cholesterol do occur, with values returning to fasting levels within 12 h (Evans and Laker 1995). Rivera-Coll (1994) showed that there is a striking variation in serum lipid concentrations, which follow a rhythmic circadian pattern. (Rivera-Col, Funtes-Arderiu et al. 1994). In the cross-sectional studies, particularly the WOLF study, it was possible to estimate this circadian effect on lipid concentrations, and the main discrepancy in lipid concentration between day and shift workers remained. Similar elevation of triglycerides among shift workers compared to day workers has been shown in a number of epidemiological studies (Orth-Gomér 1983; Knutsson, Åkerstedt et al. 1988; Romon, Nuttens et al. 1992; Lasfargues, Vol et al. 1996; Nakamura, Shimai et al. 1997; Nagaya, Yoshida et al. 2002). Unfortunately, nearly all of them lack a good estimate of the potential effect of the specific circadian rhythm on blood lipids. In only one study was a decrease seen in HDL-cholesterol among shift workers compared to day workers (De Backer, Kornitzer et al. 1987).

The mechanism of the nocturnal lipid intolerance remains unexplained but may be caused by either impaired clearance of circulating triglycerides or impaired suppression of hepatic triglyceride synthesis and secretion, or both. Lipoprotein lipase (LPL) is a key postprandial rate-limiting enzyme involved in the hydrolysis and removal of dietary triglycerides from the circulation (Lithell, Boberg et al. 1978; Arasaradnam, Morgan et al. 2002). Quite recently Arasaradnam (Arasaradnam, Morgan et al. 2002) showed decreased postprandial LPL and hepatic lipase (HL) activity in the evening compared with the morning, hence diet and meal timing are two determining factors in abnormal late evening responses. Whether bright light at night affects lipid metabolism is at present pure speculation (Arasaradnam, Morgan et al. 2002).

OUTCOMES OF ARTICLE FOUR

Cause specific mortality of diabetes

Established obesity increases the risk of developing type-II diabetes (Liese, Mayer-Davis et al. 1998). The pathogenesis of type-II diabetes has two main elements - insulin resistance and impaired beta cell function (DeFronzo, Bonadonna et al. 1992).

In the cohort study a trend for diabetes was found when shift exposure data in a pulp and paper industry were linked to the national
Discussion

Cause of Death Register. Furthermore, when the follow-up period was restricted to a short period after retirement, a stronger association between diabetes and exposure to shift work was found. This restriction amplifies occupational factors and reduces non-occupational confounding factors which may well appear in later life and contribute to the appearance of diabetes.

One earlier cohort study has shown the same development of increased age standardised distribution of diabetes with increasing number of shift years in nurses (Kawachi, Colditz et al. 1995). Hitherto, no other studies have shown such an association between diabetes and shift work.

A possible reason for the paucity of studies showing this association is the difficulty of designing good cohort studies and the need for follow-up periods long enough to detect the development of this chronic disease.

**Total mortality and cause specific mortality of CVD and stroke**

A significant increase in total mortality among shift workers was not seen. On the other hand, an increased risk of CHD was seen in workers exposed to shift work for the longest time (>30= years) and a significant increase in ischaemic stroke was seen in those exposed to shift work for the shortest time (<5 years). An overall increase in CHD and stroke mortality in shift workers was also seen. Increased risk of CHD in shift workers has been shown earlier (Bøggild and Knutsson 1999). Increased risk of stroke in shift workers has not been previously demonstrated, although a Finnish study of the role of socio-economic inequalities and occupation in cardiovascular mortality did conclude that two-shift work may have been a factor in cerebrovascular death (Virtanen and Notkola 2002).

One might imagine that all these negative influences of common diseases as CHD, diabetes and stroke would have a negative impact on total mortality for shift workers, but this could not be shown either in this or in other studies (Taylor and Pocock 1972; Bøggild, Suadicani et al. 1999), even though the metabolic factors earlier discussed in the thesis - obesity, altered lipids and the clustering of metabolic risk factors among shift workers are known to lead to diabetes, CHD and ischaemic stroke.
There may be other diseases e.g. malignancies, however, that could be more prevalent in day workers, and these could compensate for any increased mortality from CHD, diabetes and stroke in shift workers. Being able to make standard comparisons between day workers and shift workers at the same plant is an advantage. Because of the healthy worker effect, comparing a group of workers at a plant with a group taken from the general population – indirect standardisation - (Taylor and Pocock 1972) runs a much greater risk of underestimating disease prevalences.

DOES RECURRENT DISRUPTION OF THE INNATE BIOLOGICAL CLOCK BY SHIFT WORK EXPOSURE PREDISPOSE TO METABOLIC DISTURBANCES?

The last century has seen a global change of lifestyle. In many ways, the pulp and paper cohort in this thesis mirrors this period of development. The cohort study covers a period during which electricity became widely available - leading to changes in methods of production and allowing people the use of artificial light irrespective of clock times. Food became more plentiful and people began to eat snacks more often, shifting food intake toward the end of the day. At the same time people became physically less active. In addition physical activity was no longer confined to hours of daylight i.e. to certain clock times.

All these changes, according to a hypothesis recently put forward by Kreier et al, mean that "the environment sensed by the brain has become metabolically flattened and arrhythmic" (Kreier, Yilmaz et al. 2003). Furthermore, he proposed that an unbalanced or arrhythmic autonomic nervous system is a major cause of the metabolic syndrome. So far, no common denominator underlying the metabolic findings of visceral obesity, dyslipidaemia and cardiovascular diseases has been identified. Does a disrupted biological clock in the suprachiasmatic nucleus cause the metabolic syndrome through a hypothetical autonomic imbalance with increased parasympathetic dominance in the visceral compartment (abdomen), and increased sympathetic tone in the thoracic (blood pressure and heart rate) and movement (muscle) compartments (Kreier, Yilmaz et al. 2003)?

In other words, could the increased prevalence of obesity, which was found in the cross-sectional studies, be the result of an imbalance of the autonomic nervous system?
METHODOLOGICAL CONSIDERATIONS

The four studies in this thesis represent different working populations. Every individual included belongs to the "healthy working population" and in general all comparisons have been made between working groups (day or shift workers) or within the same group working different shifts.

Selection bias

In the intervention study 11 female nurses with a range of night work experience between 3-23 years were selected for the study. All were healthy and highly motivated.

Validations carried out on the participants in the VIP-study showed that there were very small differences between the participants and the non-participants, indicating that the social selection bias was small (Weinehall, Hallgren et al. 1998). However, unemployed people with low income and younger age tended to be somewhat less well represented (The unemployed were excluded from the VIP-study.)

In the WOLF study the total rate of participation in the two factories was 94%. Characteristics of the remaining group of 6% are unknown.

In the cohort study all individuals defined as male blue-collar workers employed between January 1, 1952 and December 31, 1998 were included. Eighty individuals with an incomplete job history, 39 men older than 60 years at age at first employment and 135 untraceable individuals were excluded. The company records were well kept and of good quality, and it is very unlikely that any sizeable number of records were missing.

Information bias

Participants in the intervention study complied well with the protocol. Laboratory procedures were well managed and no data were lost to analysis.

A well structured booklet was used to collect information from the participants in both the VIP-study and the WOLF study. The
participants handed in the booklet when they came to give blood samples or to meet the nurse at the primary care unit or occupational health units. Neither of the cross-sectional studies were initially presented as a specific study to compare outcomes in relation to day and shift work exposure. This fact is important because it reduces the risk that either shift workers or day workers gave biased information. But it is possible that individual with diseases, irrespective of work form, were better able to remember and fill in the questionnaire. Exposure to day work or shift work in the VIP-study was validated (table 1) and in the WOLF-study confirmed by the company personnel register.

In the cohort study, information about shift exposure was obtained from the first date of employment. Exposure was categorised according to job title and work place. A few individuals were excluded because of uncertainty about their work history. Shift patterns were divided into six types. ICD-classifications have been revised five times during the fifty years of follow up, and every new edition of the ICD classification has provided a more detailed break-down of each diagnosis. This means that older diagnosis data tends to be cruder. A strictly defined range of diagnostic codes was used to classify specific causes of death (CHD, ischaemic stroke and diabetes) – see appendix to the cohort study. Uncertainty could not be eliminated entirely, but from a global perspective the quality of the Swedish Register of Death is generally regarded as high. It seems highly implausible that previous patterns of shift work could have led to bias in classification of cause of death, and absence of a specific cause of death is unlikely to have occurred more often in any particular group.

Confounding factors

A defined investigation protocol was used by the nurses as documented in the first article. Potential confounding factors were reduced as each individual acted as her own control and as daily food intake was kept constant, (assuming that no subject ate more or less than was specified).

In the three epidemiological studies potential confounders are mitigated by restriction (sexes, age groups) or by statistical techniques such as direct age standardisation and logistic regression modelling (age, socio-economic factors, physical activity, current smoking, low social support and job strain).
Discussion

In the VIP study (Paper 2) both sexes were stratified into different age groups and analysed separately. With regard to outcomes such as obesity, high triglycerides and low HDL-cholesterol, the data were adjusted by age and socio-economic status. Direct age standardisation was used to calculate the relative risks when comparing a number of clustering metabolic risk factors in shift workers and day workers. In the WOLF study (Paper 3) only males were included in the analysis, and outcomes such as obesity, high triglycerides and low HDL-cholesterol were adjusted for age, socio-economic status, physical activity, current smoking, low social support and job strain.

The historical study (Paper 4) is restricted to blue-collar males and the data are directly age standardised. There was no available information about any other potential major confounders. However, some adjustment was made for confounders in this cohort by the cross-sectional WOLF study (Paper 3) which looked at cohort employed in 1996-1997. Additional knowledge was thus gained about potential confounders e.g. socio-economic status, physical activity, current smoking, low social support and job strain. Of course this period reflects only a very short part of the whole cohort period, but it is unlikely that historical trends in Swedish society as a whole would be more evident in one group of shift workers than another. Very few individuals were excluded from the cohort because of uncertain or missing data on follow-up. The main reasons for this were the stability of the local population and the high quality of the company personnel files.
CONCLUSIONS

- Obesity, measured as increased BMI or increased waist/hip ratio, is more common in shift workers, and precedes any rise in serum lipids.

- Unfavourable metabolic risk factors such as high triglycerides and low HDL-cholesterol are more common in shift workers.

- Other metabolic risk factors included in the metabolic syndrome, such as hypertension or impaired glucose tolerance are not more common in shift workers.

- Meal intake in a non-phase-adjusted shift worker gives a higher glucose and insulin response, especially in the late evenings.

- Total mortality is not affected by shift work.

- The cause-specific mortality diagnoses of CHD, diabetes and stroke are all affected by shift work exposure.
FUTURE CONSIDERATIONS

The enormous increase in obesity in the Western World and in developing countries with a western lifestyle is the focus of increasing concern. All the studies in this thesis have focused on specific metabolic aspects of shift work exposure. My aim has been to identify and investigate issues that have been raised by earlier work on the metabolic effects of working shifts. I hope that this work has confirmed some previous findings and produced some new ones. One of the major findings of this thesis is that shift work seems to play a role in the worldwide epidemic of obesity. It is important, therefore, that research continues in this field, as an increasing proportion of the world population is exposed to non-regular working hours.

Very few of the participants in any of the four studies are at the moment entitled to specific medical surveillance on account of night work. In my opinion, the present Swedish guidelines (The Swedish National Board of Occupational Safety and Health 1997) for night workers "make an ineffectual statement" and ought to be revised.
ACKNOWLEDGEMENTS

Doing my own academic research was something I rarely considered during my working life. However, ever since I was a medical student at the Karolinska Institute/Huddinge hospital in the seventies I have always enjoyed taking on new challenges in my clinical work, and "Täckes prov" (Professor Gunnar Birke) has always been "my way as a clinician".

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