

IN-DEPTH REVIEW: SHIFT WORK

Health disorders of shift workers

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Abstract The effects of shift work on physiological function through disruption of circadian rhythms are well described. However, shift work can also be associated with specific pathological disorders. This article reviews the evidence for a relationship between specific medical disorders and working at night or on shift systems. The strongest evidence exists for an association with peptic ulcer disease, coronary heart disease and compromised pregnancy outcome.

Key words Cardiovascular diseases; gastrointestinal diseases; health; medical surveillance; night work; pregnancy; shift work.

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Introduction

Immediate disturbances associated with shift work are symptoms such as sleep disturbances, fatigue, 'jet lag' and gastrointestinal malfunction. These symptoms are often short term or related to specific phases of the work schedule, especially to periods of night work. During day shifts or in longer vacations, the symptoms might disappear. Sometimes, the symptoms reflect a serious chronic disease process. In this review, the focus is on major disease related to shift work. Sleep disorders and risk of accidents, however, are covered in related reviews in this issue [1,2].

Mortality

Today, no evidence exists showing that shift work affects longevity. Only two studies have addressed all-cause mortality in shift workers. A British study followed 8603 male manual workers from 1956 to 1968 [3]. In total, 1578 deaths were notified. Indirect standardization was used for comparisons. The number of deaths in each group was divided by the expected number of deaths calculated from rates in the general population. The observed and expected number of deaths in day workers were 736 and 756.4, respectively. The corresponding figures for shift workers were 722 and 711.4, and for

ex-shift workers 120 and 100.9. The authors concluded that 'shift work would appear to have no adverse effect upon mortality'. A Danish cohort study of 5249 reported general mortality in 1123 shift workers and 4084 day workers, who were followed for 22 years [4]. The relative death risk was 1.1 [95% confidence interval (95% CI) = 0.9–1.3] for shift workers after adjustment for age and social class.

Gastrointestinal disease

Gastrointestinal symptoms are very common in the general population. However, gastrointestinal disorders are more common in shift workers than in day workers [5]. Common complaints are pain and alterations in bowel habits, especially constipation and diarrhoea. Shift workers may experience temporary variation in bowel habit in association with night work. Thiis-Evensen named ulcers the occupational disease of shift workers, and Harrington [6] was of the same opinion in his influential review from 1978. However, most studies on the association between shift work and peptic ulcer disease are old, and in these early papers the diagnosis was often not verified through X-ray or endoscopy. Since many ulcers are asymptomatic, a number of cases will be missed if the diagnosis is based on symptoms only. However, an early case-referent study of 1193 cases collected from 1930 to 1940 in Sweden showed that peptic ulcer disease was more common in occupations where shift work and night work were common: taxi and truck drivers, travelling salesmen, tram-car and railway employees, sailors, factory workers, postmen, printers

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and night watchmen [7]. The diagnosis was based on X-ray examinations in all cases except 10, where diagnosis was made at autopsy. A Japanese study of high quality examined 11 657 employees in factories, banks and schools [8]. The examinees suspected to have abnormal roentgenologic findings by mass examination were asked to undergo a precise examination by endoscope. The prevalence of gastric ulcers was 2.38% in shift workers as compared with 1.03% in day workers. For duodenal ulcers, the prevalences were 1.37% and 0.69% for shift workers and day workers, respectively. Thus, the relative risk of duodenal ulcers was doubled in shift workers compared with day workers.

In summary, there is strong evidence linking shift work to peptic ulcer disease.

Cardiovascular disease

Cardiovascular diseases (CVD) may have many different causes. During the past 15 years, evidence has accumulated indicating that conditions in the work environment contribute to the aetiology of CVD. Among the work-related risk factors are chemical compounds, noise and vibration. In addition, a number of psychosocial factors, e.g. organization of work, work schedules and behaviour, are associated with an increased risk of CVD. In a paper published in 1999, 17 studies on shift work and CVD were reviewed [9]. Thirteen of these studies were longitudinal: four used case-referent design and nine were cohort studies. It was concluded that shift workers had a 40% excess risk for CVD compared with day workers. The longitudinal studies, which are published in Medline-indexed journals, are briefly reviewed below.

Alfredsson *et al.* [10] carried out a study of 334 cases with myocardial infarction and 882 controls, who were selected randomly from the general population in the same region. The shift-work exposure was assessed from the occupational code, and from an interview of 14 500 people belonging to a random sample of households in Sweden. The results showed that shift work was associated with myocardial infarction [age-standardized relative risk (RR) = 1.25, 95% CI = 0.97–1.62]. A British nested case-referent study [11] investigated the mortality of employees who had worked in a factory producing nuclear fuel elements. In total, 467 cases with ischaemic heart disease as cause of death were compared with 467 surviving controls. The odds ratio (OR) for shift workers during the period starting 10 years after shift work began, and after adjustment for height, body mass index (BMI), blood pressure, smoking, duration of employment and job status, was 0.90 (90% CI = 0.68–1.21). However, an obvious problem with that study was the different prevalences of traditional risk factors at baseline. At the time of employment, the shift workers had lower blood

pressure and a lower prevalence of overweight workers than did the day workers. Therefore, this could explain the low risk in shift workers. A nested case-referent study (163 cases and 781 matched controls) of male workers at four heavy equipment plants in the USA did not demonstrate any increased risk of cardiovascular mortality in shift workers [12]. In a Swedish case-referent study of 2006 cases and 2642 controls, it was shown that the myocardial infarction risk was associated with shift work both in men (OR = 1.3, 95% CI = 1.1–1.6) and women (OR = 1.3, 95% CI = 0.9–1.8).

A mortality study by Taylor and Pocock [3] included 8603 male manual workers from 10 organizations in England and Wales. They were followed from 1956 to 1968. The authors draw the conclusion that there was no association between shift work and cardiovascular mortality, although their data did demonstrate an increasing trend, with a standardized mortality ratio (SMR) of 92 for day workers, 102 for shift workers and 132 for shift work drop-outs. A German historical cohort study followed 370 male shift workers and 270 day workers employed in a chemical industry [13]. The incidence of CVD during follow-up (from 1966 to 1977) was 1.4/100 person-years in day workers, 1.8/100 person-years in permanent shift workers, 2.3/100 person-years in shift workers changing to day work (before change) and 5.8/100 person-years in shift workers changing to day work (after the change) (approximate figures are extracted from figure 3 in the original report). Thus, the highest RR (4) was demonstrated for ex-shift workers.

A cohort study of 394 shift workers and 110 day workers working at a paper mill demonstrated a dose-response relationship between years of shift work and coronary heart disease [14]. However, the study population was small, and it was therefore not possible to adjust for major potential confounding variables, other than age and smoking. A similar study design and analysis was performed in an American study of 79 000 nurses followed for 4 years [15]. That study also showed a dose-response relationship between years of shift work and coronary heart disease. The results were controlled for confounders, e.g. smoking, BMI, hypertension, diabetes, hypercholesterolaemia, alcohol intake and physical activity.

In a Danish study, the relative risk of being admitted to hospital due to ischaemic heart disease was measured in a cohort of 1 293 888 men [16]. Information on occupation was used to classify each subject into different shift work exposure categories. The results showed that, compared with occupational groups having day work only, men in occupations with frequent night and early morning work had an excess standardized hospitalization ratio of 193, occupational groups with late evening work had an excess risk of 216, and groups working in rosters

covering 24 h services had an excess risk of 174. Tenkanen *et al.* [17] followed a cohort of 1804 industrial workers in the Helsinki Heart Study, a 5 year placebo-controlled coronary prevention trial on middle-aged men. When shift workers were compared with day workers, the age-adjusted RR of coronary heart disease was 1.5 (95% CI = 1.1–2.1). After adjustment for lifestyle factors, blood pressure and serum lipids, the RR was 1.4 (95% CI = 1.0–1.9).

A Danish cohort study of 5249 men aged 40–59 years did not find an increased risk among shift workers as compared with day workers [4]. The authors question previous findings on an association between shift work and CVD, and hypothesize that previous positive findings are due to insufficient control for social class. A problem with this study is the time window during which the study population was followed. In 1970–1971, when the study started, workers between 40 and 59 years old were included. In this age group, a selection has already taken place: workers with bad adaptation to shift work have already been transferred to day work. Therefore, the shift workers were a ‘survivor population’. The cohort was followed until 1993. In 1993, the age of the population was between 62 and 82 years. Most deaths occurred at very high age, and it is probable that other important factors than work schedules were responsible for the cause of death.

To summarize, there is rather strong evidence in favour of an association between shift work and coronary heart disease.

Cancer

Few studies have addressed the association between cancer and shift work. The mortality study by Taylor and Pocock [3] reported a significantly increased incidence of neoplasms in shift workers compared with the general population (SMR = 116). Recently, a Danish case-control study [18] reported an increased risk of breast cancer among 30- to 54-year-old women who worked predominantly at night (OR = 1.5, 95% CI = 1.3–1.7). The results were adjusted for age, social class, age at birth of first child, age at birth of last child and number of children. Epidemiological studies of women with various kinds of shift and night work have demonstrated an elevated risk of breast cancer; occupational groups include flight attendants, nurses, and radio and telegraph operators. However, other carcinogenic exposures could have been responsible for the increased risk in specific occupations, e.g. ionizing radiation in airline cabin attendants.

There has been a discussion on whether low levels of the hormone melatonin might increase the risk of specific cancers [19]. This hypothesis has been supported by studies showing decreased risk of cancer in blind people.

However, today there is no conclusive evidence that night work *per se* increases the risk of cancer.

Diabetes and metabolic disturbances

Theorell and Åkerstedt [20] demonstrated that serum concentrations of potassium, uric acid, glucose, cholesterol and total lipids increased during night work. The levels fell to normal upon return to day work. The authors suggested that these results indicated that night work is catabolic, which in turn could have long-term cardiovascular health effects. Another study [21], of 46 policemen, demonstrated that the direction of shift rotation could affect metabolic variables. During clockwise shift rotation, serum triglycerides, glucose and uric acid were lower as compared to during counterclockwise rotation. A number of epidemiological studies have shown that shift workers have higher levels of triglycerides than day workers.

Only a few studies have assessed coagulation factors in relation to shift work. Peternel *et al.* [22] showed that plasminogen activator and tissue plasminogen activator inhibitor had lower amplitude among shift workers. One study reported higher fibrinogen levels among shift workers than day workers [23].

Studies on weight and BMI in day and shift workers have yielded inconsistent results. One study, which found similar body mass indices in day and shift workers, reported more centrally disposed adipose tissue in shift workers [24]. Niedhammar *et al.* [25] followed 469 nurses for 5 years, and found that weight gains (especially those >7 kg) were more frequent among nurses on night work than on daytime work. A study by van Amelsvoort [26] found an association between BMI and duration of shift work experience. A number of studies, however, have not been able to confirm weight differences between shift and day workers (for a review see [9]).

Only a few studies have reported prevalence of diabetes mellitus in relation to shift work. Koller *et al.* [27] investigated 300 workers at an Austrian oil refinery and found that the prevalence of endocrine and metabolic disease was 3.5% in shift workers, 1.5% in day workers, and 2.8% among drop-outs. A Japanese study [28] found a prevalence of 2.1% in subjects who worked all three shifts, compared with 0.9% in day workers. Kawachi *et al.* [15] conducted a prospective study of shift work and risk of coronary heart disease in female nurses. The age-standardized prevalence of diabetes was found to increase with increasing exposure to shift work: never, 3.5%; 1–2 years, 3.2%; 3–5 years, 3.5%; 6–9 years, 4.4%; 10–14 years, 5.0%; ≥15 years, 5.6%.

A recent study by Nagaya *et al.* [29] examined the relationship between shift work and markers of insulin resistance. They found that all markers of insulin resist-

ance were more common in shift workers than in day workers in the age group <50 years.

Taken together, these results indicate that shift work might have an impact on metabolic variables, and also be a risk factor for diabetes, although the evidence is not conclusive.

Pregnancy

The relationship between work conditions and pregnancy outcome has been reported in three studies based on the Montreal survey of ~22 700 single live births. The results showed association between shift work and low birth weight [30,31]. In the service sector, MacDonald *et al.* [30] also found a significant relationship between shift work and preterm birth. Based on the same data set, one paper reported fetal death in relation to work in pregnancy. They found an increased risk of spontaneous abortion among shift workers (RR = 1.25) [30]. A Chinese study [32] reported that the OR of shift work was 2.0 (95% CI = 1.1–3.4) for preterm birth and 2.1 (95% CI = 1.1–4.1) for low birth weight. The estimated effect of rotating shift work on birth weight was –79 g. A Swedish study showed an association between shift work and low birth weight [33]. That study also reported increased risk of miscarriage in women who worked irregular hours or rotating shifts compared with day workers (RR = 1.44, 95% CI = 0.83–2.51). Uehata and Sasakawa [34] conducted a study of 2264 women and showed that irregular menstruation and abortions were more common in shift workers. Mamelle *et al.* [35] found that shift work was associated with an increased risk

of premature births. The potential association between shift work and congenital malformations has not been addressed in previous studies.

To summarize, there is rather strong evidence in support of an association between shift work and pregnancy outcome in terms of miscarriage, low birth weight and preterm birth. Even in the absence of further proof, it would be prudent for women to avoid or be relieved of such work during pregnancy.

Exacerbation of existing disorders

Many biological variables follow a circadian rhythm, and shift work can interfere with disorders involving these variables. The dose–response patterns of many drugs also follow a circadian pattern. Even if the shift worker takes a drug at the same clock time every day, the resulting biological effect can differ, due to desynchronization of the internal body clock. Sleep deprivation can also modify medical disorders, and the effectiveness of medications. For example, epileptics might experience more frequent seizures, due to sleep deprivation [36]. Diabetes and asthma are other disorders in which work schedules might affect disease status.

Mechanisms

A key issue when discussing health problems in shift workers is the role of disturbed circadian rhythm. It is not clear whether repeated displacement of circadian rhythms increases the risk of CVD. However, a possible mechanism linking shifted circadian rhythm with metabolic

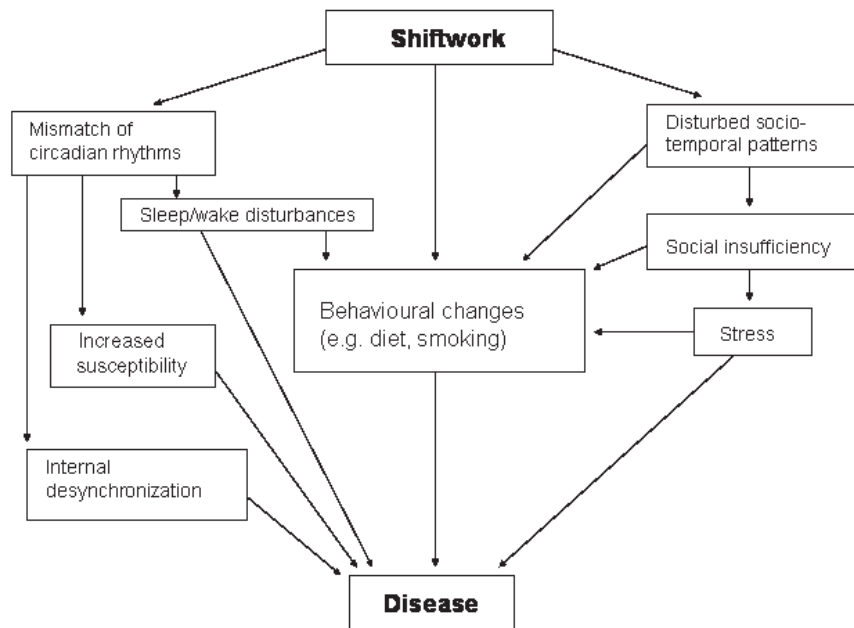


Figure 1. Disease mechanisms in shift workers (from [40]).

disease and CVD has been suggested recently. Hampton *et al.* [37] found that after phase shift there were significantly higher postprandial glucose levels than before. Similar results were obtained for insulin. Ribeiro *et al.* [38] conducted a study with similar design, where the study subjects had a high fat content pre-meal, and this time no change in postprandial glucose and insulin responses was demonstrated. These findings suggest that both the quality of the food and the timing of food intake could play a role for the metabolic response.

Health problems in shift workers could also be mediated by sleep problems. The health effects of sleep deprivation are basically unknown, but recent findings have indicated that sleep deprivation could affect glucose tolerance [39].

Lifestyle and stress are also potential mediators of disease in shift workers. The model in Figure 1 summarizes possible mechanisms of disease in shift workers.

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