Adverse health effects of shift work and shift work sleep disorder

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Shift work has existed for nearly the entirety of recorded human history, albeit limited to the realm of the common soldier or sailor prior to the late 19th century. The invention of commercially practical incandescent lighting in 1879 is often cited as the factor that allowed widespread shift work to become a reality. Since then, the prevalence of shift work among the general population has steadily increased. Today, as much as 20% of the U.S. working population can be labeled as shift workers. Although shift work has led to dramatically increased overall productivity within industrialized society, there is a growing acknowledgement that this benefit has not come without a cost to the worker.
The symptoms of insomnia and excessive somnolence in association with some degree of social, occupational, or other impairment are collectively known as shift work sleep disorder (SWSD). However, shift work has been associated with a variety of other adverse health effects as well. A number of factors have been implicated in the pathogenesis of disease in shift workers, including circadian rhythm disruption, sleep/wake disturbances, and internal desynchronization. These pathologic alterations are thought to be largely related to exposure to artificial light at night. Shift work is also purported to act as an oxidative stressor, which is particularly relevant to the pathogenesis of cardiovascular disorders. Social factors such as disturbed sociotemporal patterns and social insufficiency also play a role in disease development and progression by inducing stress and, subsequently, promoting maladaptive behaviors. The extent to which symptomatic circadian rhythm disruption resulting from shift work contributes to the pathogenesis of disease has been less extensively studied.

With some epidemiologic studies estimating that insomnia or excessive sleepiness is present in 26% of night workers and 32% of rotating shift workers, SWSD deserves special scrutiny when the adverse health effects in shift work are considered. The present article reviews the direct effects of shift work on the development of various disease states, as well as the impact of shift work on pre-existing comorbid conditions.

**Gastrointestinal disorders**

The relationship between gastrointestinal illness and shift work, even in the absence of symptomatic circadian rhythm disturbance, has been long recognized. In 2004, a cross-sectional study by Caruso et al reported an increase in gastrointestinal symptoms (eg, abdominal pain, constipation, diarrhea, heartburn, indigestion, loss of appetite, nausea) in individuals working more than 30 night-shift hours in a 28-day period. The researchers also found a 3-fold increase in the risk of a gastrointestinal diagnosis (eg, colon polyps, stomach ulcers, ulcerative colitis) in evening-shift workers.

Another study showed that approximately 50% of permanent night-shift workers have appetite disturbances or gastrointestinal problems. Although these problems are likely caused, in large part, by the difficulty of obtaining nutritious meals and the lack of a customary social environment for food consumption, sleep disturbances are also thought to play a role. Sleep deprivation induces alterations in secretion of leptin and ghrelin (hormones responsible for the regulation of satiety and appetite, respectively), and dysregulation of these hormones leads to a tendency to overeat.

Other proposed factors in the association of gastrointestinal illness with shift work include increased uses of caffeine, tobacco, and alcohol by shift workers as coping mechanisms. The loss of synchronization between the intrinsic circadian rhythm and rhythmic gastrointestinal function (ie, gastrointestinal motility, enzyme activity) almost certainly plays a role as well.

**Peptic ulcers**

In 1958, Thii-Evensen proclaimed peptic ulcer disease to be the occupational disease of shift workers. Indeed, several large-scale studies have demonstrated statistically significant increases in the risk of gastric and duodenal ulcers in night-shift and rotating-shift workers compared to day workers. As reported in a large cohort study by Sugisawa and Uehata in 1998, the risk of peptic ulcer disease in permanent night-shift workers was twice the risk in daytime workers (relative risk [RR], 2.0; 95% confidence interval [CI], 1.49-2.67). An even stronger association (odds ratio [OR], 4.55; 95% CI, 2.47-8.37) was demonstrated in shift workers who reported symptoms of circadian rhythm disturbance (eg, insomnia, excessive sleepiness). It is unclear whether this association reflects the influence of a distinct pathophysiologic process leading directly to the development of peptic ulceration or the propagation of an environment in which preexisting or latent disease is exacerbated. Zober et al demonstrated in a 1998 cross-sec-
A reflux disease questionnaire score of more than 12 as a more rigorous definition nearly 13% among the workers. Using lence of GERD in this population was published a large-scale epidemiologic study of chemical company employees that positive serology results for Helicobacter pylori were more prevalent in shift workers than in day workers (RR, 1.20; 95% CI, 1.10-1.32). However, the prevalence of ulcer disease reported in that study was not statistically significantly different between these 2 groups. In contrast, a study by Pietroosti et al in 2006 comparing day and night workers for H. pylori positive results showed a statistically significant increased prevalence of duodenal ulcer in night workers (OR, 3.96; 95% CI, 2.10-7.47) as detected with upper gastrointestinal endoscopy.

On the basis of the findings of these similar studies, dyspeptic shift workers should be screened for H. pylori. Furthermore, in an effort to reduce morbidity from ulcer disease, consideration should be given to the eradication of H. pylori in this population.

Gastroesophageal reflux disease

The association of gastroesophageal reflux disease (GERD) with shift work is less extensively studied than that of peptic ulceration. In 2008, Li et al published a large-scale epidemiologic investigation of GERD in workers in China. On the basis of a validated questionnaire (Reflux Disease Questionnaire) used to identify GERD symptoms, the prevalence of weekly heartburn or acid regurgitation was nearly 13% among the workers. Using a Reflux Disease Questionnaire score of more than 12 as a more rigorous definition of a GERD diagnosis, the prevalence of GERD in this population was more than 7%.

Li et al cited the bland diet typical of the region (Zhejiang province, in eastern China) as the reason for the comparatively low prevalence of GERD, compared to that seen in Western industrialized countries (where GERD prevalence is estimated to be more than 25%). However, in a multi-ple logistic regression analysis of independent risk factors for GERD symptoms, Li et al reported that night-shift work was significantly associated with GERD (OR, 1.38; 95% CI, 1.11-1.71) even when adjustments were made for age, work burden, marital status, and eating habits (eg, consumption of greasy or sweet food, excessive eating).

Inflammatory bowel disease

Inflammatory bowel disease (IBD), especially ulcerative colitis and Crohn disease, is negatively impacted by sleep disruption. Shift workers with these conditions may complain of poorer control of their symptoms and worse quality of life than other individuals with the same conditions. Individuals with IBD report prolonged sleep latency, increased sleep fragmentation, and generally reduced sleep quality—subjective complaints that correlate well with changes in polysomnographic parameters. Thus, shift workers who have both IBD and sleep disruption may have more pronounced sleep-related complaints than individuals without IBD.

Not only does IBD cause sleep disruption and potentially worsen excessive somnolence, but some authors have suggested that individuals with irregular work schedules may be at increased risk for IBD. In 1990, Sonnenberg investigated the distribution of IBD among workers in various occupations, finding that a higher risk for IBD was conferred by working in environments with artificial lighting or air conditioning, as well as by working irregular schedules (eg, rotating shift work).

Irritable bowel syndrome

Irritable bowel syndrome (IBS), the most common functional bowel disorder, is characterized by chronic bouts of abdominal pain, bloating, and alteration of bowel habits (ie, alternating constipation and diarrhea). Individuals with IBS have increased healthcare use and worse quality of life compared to individuals without IBS. As reported in a 2010 study by Nojkov et al, nurses who worked day, night, or rotating shifts at a single medical center completed a series of questionnaires regarding their abdominal problems, quality of life, and sleep quality. The study results showed that participation in shift work, especially rotating shift work, was associated with the development of IBS and abdominal pain—indeed, modestly associated with IBS. Sleep complaints were also independent risk factors for IBS, especially somnolence (OR, 3.64; 95% CI, 2.19-6.05) and insomnia (OR, 2.05; 95% CI, 1.22-3.45).

Metabolic disorders

Many studies have linked shift work, circadian rhythm disturbance, and sleep deprivation to a number of metabolic and endocrine disturbances. This finding led the authors to suggest that shift work represents a catabolic state, and that long-term cardiovascular sequelae could ensue. In 1976, Theorell and Akerstedt demonstrated that night workers had increased serum concentrations of glucose, potassium, uric acid, cholesterol, and total lipids, compared to controls—changes that were reversed by a return to a standard work schedule. This finding led the authors to suggest that shift work represents a catabolic state, and that long-term cardiovascular sequelae could ensue.

In 2008, Biggi et al published results suggesting that permanent night workers had statistically significant higher body mass index (BMI), serum total cholesterol levels, and triglyceride levels, as well as greater use of antihypertensive, hypoglycemic, and lipid-lowering medications, compared to day workers. In another study, rotating shift work was found to be an independent risk factor for metabolic syndrome in European men (OR, 1.51; 95% CI, 1.01-2.25).
when corrected for age and physical-activity variables. When corrected for age and physical-activity variables.

Evidence linking diabetes mellitus to shift work is less robust than the evidence for other conditions previously described. A 1983 study demonstrated that the prevalence of diabetes mellitus increased with shift work, particularly in study participants with prolonged exposure to shift work (i.e., >10-15 years). A more recent study, published in 2002, found that elevated markers of insulin resistance were most common in shift workers younger than 50 years. However, a 2005 study from Japan that investigated the incidence of new-onset diabetes mellitus in factory workers over an 8-year period indicated that no statistically significant difference existed between day and night workers.

The influence of shift work on the control of diabetes mellitus remains unclear. In a study of insulin-requiring patients with diabetes mellitus who worked in a single factory, the control of diabetes in shift workers was no different from that in day workers. However, a trend toward worsening diabetes control was noted in rapidly rotating shift workers when compared with those working slowly rotating shift schedules.

Despite these findings, it appears certain that regular food intake and appropriate timing of medications can be challenging for individuals with diabetes mellitus who are engaged in shift work, and this challenge may lead to impaired blood sugar control and a greater burden of diabetic complications.

Immune disorders
Sleep and the innate immune system are intertwined in complex ways, with the function of the immune system being influenced in a pronounced manner by changes in sleep and circadian rhythm. Conversely, acute and chronic inflammatory states are known to disrupt the normal sleep cycle, and patients with inflammatory conditions often complain of increased somnolence and fatigue. Some inflammatory cytokines, such as interleukin 1 (IL-1) and tumor necrosis factor (TNF), are known to promote slow-wave sleep. Blocking the effect of either of these substances has been shown to inhibit both spontaneous sleep and the sleep-rebound phenomenon that is normally seen after sleep deprivation. Other proinflammatory cytokines, such as IL-6, have been shown to suppress rapid-eye-movement sleep and to promote wakefulness. Sleep restriction and insomnia are associated with elevated serum levels of IL-6, TNF, and C-reactive protein, suggesting that sleep deprivation is—in a measurable sense—a proinflammatory state. Some authors have also posited that increased slow-wave sleep is an acute phase response to an inflammatory condition.

Despite the growing body of evidence concerning the effects of shift work and circadian rhythm disruption on immune function, effects on autoimmune disorders have rarely been studied. A 2006 study by Magrini et al demonstrated statistically significant increases in altered antithyroid peroxidase antibodies in shift workers, as well as a higher incidence of subclinical autoimmune hypothyroidism. A study investigating occupational risk factors for systemic lupus erythematosus found a weak association between this condition and shift work, barely missing statistical significance (OR, 1.6; 95% CI, 0.99-2.7).

Cardiovascular disease
Cardiovascular changes in individuals engaged in shift work have been extensively investigated for decades. In a 1999 meta-analysis of 17 studies examining the association between cardiovascular risk and shift work, shift workers were estimated to have a 40% increased risk for cardiovascular disease.

The pathomechanisms contributing to the development of cardiovascular disease in individuals with SWSD are multifactorial. The circadian system is known to modulate markers of cardiovascular risk, such as sympathetic activity, cardiac vagal tone, heart rate, blood pressure, and serum cortisol levels. In fact, the circadian cycle has been shown to influence autonomic cardiovascular function independent of environmental and behavioral stressors. Furthermore, platelet aggregation appears to be under the influence of circadian control, peaking in the morning and likely contributing to the phenomenon of increased cardiovascular events in the daytime hours.

Hypertension
When normal diurnal fluctuations in blood pressure and pulse become chronically disrupted by circadian misalignment, hypertension and its cardiovascular sequelae are more likely to develop. Although there is some conflicting evidence regarding the prevalence and overall risk of hypertension in shift workers, many studies have confirmed this association. In the 2011 prospective cohort Nurses’ Health Study II, investigators demonstrated that hypertension was significantly more common in shift workers who were African-American women than in shift workers who were white women (hazard ratio [HR], 1.81; 95% CI, 1.14-2.87). Another cohort study, published in 2005, found that among Japanese men who were laborers with mild hypertension, shift workers were significantly more likely than day workers to progress to severe hypertension (OR, 1.23; 95% CI, 1.05-1.44) or severe diastolic hypertension (OR, 1.28; 95% CI, 1.07-1.52) over a 10-year period.
**Ischemic heart disease**

Although early studies of ischemic heart disease (IHD) in shift workers were inconclusive or suggested a lack of association, more recent studies have found evidence to the contrary.\(^1\) Whether the influence of shift work is related to dietary and behavioral changes, stress, or circadian rhythm disruption remains unclear.

In 1997, an ancillary study using data from the Helsinki Heart Study found that, compared to day workers, shift workers had an increased risk of coronary disease when adjusted for blood pressure, lifestyle factors, and serum lipid levels (RR, 1.38; 95% CI, 1.01-1.89), with a mean follow-up of 5.6 years.\(^3\) The authors proposed a direct stress-related mechanism as a contributing etiologic factor on the basis of results of a psychosocial questionnaire used in the study. In 1999, another study found a similar risk of myocardial infarction in shift workers, particularly in those aged 45 to 55 years (men: OR, 1.6; 95% CI, 1.1-2.4; women: OR, 3.0; 95% CI, 1.4-6.5).\(^4\)

However, in that study the role of job-related stress did not appear to be statistically significant. Other studies suggest that duration of shift work and a rotating-shift schedule are also linked to the risk of IHD.\(^4\)

Despite the findings of these studies, it appears that cardiovascular mortality is not influenced by shift work, though the available data are limited.\(^2\) It appears certain, however, that a greater index of suspicion for IHD is required in the primary care of shift workers because of their maladaptive behaviors related to stress management. Special attention should be given to lifestyle modification and stress management in these individuals.

**Cancer**

The International Agency for Research on Cancer, an arm of the World Health Organization, coordinates and conducts research on the causes of cancer in human beings and maintains a series of monographs on known or suspected carcinogens. These carcinogens are categorized on the basis of level of evidence linking their exposures to carcinogenesis. Shift work that involves circadian rhythm disruption has been classified since 2007 as a group-2A carcinogen, meaning that there is limited evidence of carcinogenicity in humans but sufficient evidence of carcinogenicity in experimental animals.\(^3\) To place this statement into context, other exposures in group 2A include ultraviolet radiation (A, B, and C), inorganic lead, and polychlorinated biphenyls, all of which have a general scientific consensus implicating them in carcinogenesis.

The mechanisms by which circadian rhythm disruption increases the risk of cancer include reduced secretion of melatonin (a hormone known to have direct and indirect tumor-suppressing properties),\(^4\) disturbance of reproductive hormones,\(^4\) and stress-related cortisol secretion and its resultant depression of immune function.\(^4\)

Changes in melatonin secretion also cause the phenomenon of phase shift, in which loss of synchrony occurs between rhythmic bodily functions and the sleep/wake cycle. This loss, in turn, is thought to alter the control of cell and tissue proliferation.\(^4\)

Reduced vitamin D production and lifestyle changes associated with shift work (but not necessarily with circadian rhythm disruption) may also play roles.\(^3,4\)

Although the relationship of an increasing number of malignancies to SWSD is currently being investigated, only the 3 most common of these (breast, colorectal, and prostate) are reviewed in the following text.

**Breast cancer**

A systematic review and meta-analysis on the association between shift work and breast cancer was published in 2005.\(^9\) The authors extracted data from 13 studies that were published between 1995 and 2005 of which 7 examined the association in female airline cabin crews and 6 of which used other female night-shift workers. The aggregate estimate of risk of breast cancer with shift work for all studies combined was 1.48 (95% CI, 1.36-1.61), though some evidence suggested the influence of confounding variables resulting from inadequate adjustment for risk factors. Similar risks existed in subgroup analyses of airline cabin crews and other night-shift workers (1.44 and 1.51, respectively). Tests for publication bias found no evidence of bias in the combined data.\(^9\)

The impact of different shift systems (evening, night, or rotating shifts) on breast cancer incidence was examined in a 2011 study.\(^30\) The results suggested that individuals working rotating day-night shifts (ie, those most likely to have circadian rhythm disruption) had the highest risk of breast cancer (OR, 2.6; 95% CI, 1.8-3.8). By comparison, evening workers did not have an increased risk of breast cancer (OR, 0.9; 95% CI, 0.4-1.9).\(^30\)

**Colorectal cancer**

An ancillary study of colorectal cancer risk using data from the Nurses’ Health Study determined that women who worked 3 or more night shifts per month for 15 years or more had a 35% increased risk of colorectal cancer (RR, 1.35; 95% CI, 1.03-1.77) compared to day workers.\(^31\) Less than 15 years of shift work did not significantly alter colorectal cancer risk. These results were adjusted for numerous covariates, including age, body mass index, diet, and smoking history. When considered separately, the incidence of cancer...
in the colon and rectum was not significantly different after any duration of shift work.51

Whether the same association between shift work and colorectal cancer applies to men is unknown, but it is plausible to assume that male shift workers could be at an even higher risk given the already increased colon cancer risk among men. The results of this study suggest that a heightened level of suspicion of colorectal cancer is warranted in long-time shift workers, and that screening should be emphasized in this population.51

**Prostate cancer**

Limited data exist on the risk of prostate cancer in shift workers. A single prospective cohort study of men in Japan found that rotating shift work was associated with a statistically significant increased risk of prostate cancer compared to day-shift work (RR, 3.0; 95% CI, 1.2-7.7), with a mean follow-up period of 8 years.52 These results were adjusted for a broad range of covariates, including age, family history of prostate cancer, and smoking and alcohol history. Permanent night-shift workers had no demonstrable increase in prostate cancer risk.52

**Reproductive issues**

Menstrual irregularities and subfertility are more common in women who are shift workers than in women who work standard schedules. A study of 68 night-shift nurses of child-bearing age demonstrated that 53% of the women experienced changes in menstrual function, including changes in duration and flow of menses, as well as increased pain.53 In those nurses who experienced menstrual changes, sleep latency was also significantly increased compared to those with normal cycles.53

In a European population-based study of 6630 working women aged 25 to 44 years, measures of fertility, such as time to achieve pregnancy, were compared between rotating-shift workers and permanent day or night workers.54 In a multivariate analysis, rotating-shift work was associated with a higher risk of subfertility, which was defined as requiring more than 9.5 months of unprotected intercourse to achieve pregnancy (OR, 2.0; 95% CI, 1.4-2.8). Having a male partner engaging in shift work did not impact fertility in this female population.

**Neurologic issues**

**Stroke**

Like cardiovascular disease, stroke has been associated with shift work, albeit to a lesser degree. Data from the Nurses’ Health Study was used to determine stroke risk in rotating-shift workers.55 Nurses experienced a 4% increased risk of ischemic stroke for every 5 years of rotating-shift work (HR, 1.04; 95% CI, 1.01-1.07), but only after at least 15 years of exposure. When adjusted for other cardiovascular risk factors (eg, hypertension, diabetes mellitus, dyslipidemia, smoking) and covariates (eg, alcohol use, fruit and vegetable consumption, menopausal status), this relationship reached statistical significance only after 30 years of rotating-shift work. Because this study included only women, the effect of shift work on stroke risk in men could not be estimated.55

**Seizure disorders**

An extensive body of evidence exists characterizing the relationship between sleep chronobiology and seizure disorders. As early as 1885, the sleep-wake cycle was studied as an influential factor in the occurrence of grand mal seizures (ie, tonic-clonic seizures).56 Sleep deprivation, in particular, has been identified as a precipitant of seizure activity.57 However, studies of shift workers with epilepsy have failed to demonstrate a clear association between shift work and increased seizure frequency. In addition, research has not shown that shift work contributes to the pathogenesis of new-onset seizures.56

Although studies have found no association between shift work and seizures, it seems prudent that individuals with epilepsy who engage in shift work, particularly those who complain of symptoms of sleepiness, be closely monitored for changes in the control of their condition.

**Multiple sclerosis**

Multiple sclerosis, a T-cell mediated inflammatory demyelinating condition of the central nervous system, is known to be influenced by both genetic and environmental factors. Known environmental factors include latitude, diet, smoking, vitamin D deficiency, viral infections (eg, Epstein-Barr virus, human herpesvirus 6), and occupational exposures (eg, solvents).59 Recent studies have also implicated shift work as an environmental risk factor for multiple sclerosis.

In 2011, Hedstrom et al60 published the results of 2 studies—1 reviewing the incidence of multiple sclerosis and the other, the prevalence. In the incidence study, an increased risk of multiple sclerosis was found in individuals who performed shift work for at least 3 years before the age of 20 years, compared to individuals who worked only day shifts (OR, 2.0; 95% CI, 1.2-3.6). The odds ratio for the corresponding comparison in the prevalence study was similar (OR, 2.1; 95% CI, 1.3-3.4). A weaker risk for multiple sclerosis was noted in the incidence study for individuals who had any exposure to shift work (OR, 1.2; 95% CI, 1.0-1.4). All of these findings were adjusted for age, sex, ancestry, residential area, smoking status, sun exposure habits, vitamin D level, and BMI.60
All-cause mortality

To my knowledge, no studies to date have investigated the relationship between SWSD and mortality, and few studies have examined the relationship between shift work (with or without the presence of SWSD) and mortality.

In a 1972 publication, British researchers reported mortality data from a large cohort of day-shift, night-shift, and former night-shift workers who had been followed up for more than 10 years.61 Observed vs. expected death rates from various causes were compared. Although the observed mortality from neoplasms exceeded the expected mortality from these tumors in night shift workers, there were no statistically significant differences in mortality rates between the 3 groups of workers for any cause.61

Despite the association of shift work with numerous illnesses, in addition to the increased risk of motor-vehicle accidents and occupational injuries among shift workers, shift work in and of itself has not been shown to be associated with increased risk of death. Whether circadian rhythm disturbance in shift workers bears any relationship to mortality is a potential focus for future study.

Final notes

Shift work sleep disorder occurs in approximately 10% of shift workers, potentially making it the most prevalent circadian rhythm disorder in industrialized society. Given the increasing acknowledgment of the impact of shift work and SWSD on the health of workers, further study of the health effects of shift schedules is needed. Most studies to date have had limited periods of follow-up, with many findings suggesting that longer duration of shift-work exposure has more clinically significant effects. In addition, the apparently more pronounced health impact of the rotating shift should prompt further investigation.

Education of employers and employees about the potential health risks associated with various shift schedules may provide substantial benefits to society in terms of more effective screening strategies, reduced costs and use of healthcare resources, and improvements in overall productivity.

References


