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Working Time Society consensus statements: Evidence-based effects of shift work on physical and mental health

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Abstract: Potential effects of shift work on health are probably related to the misalignment between the light-dark cycle and the human activity-rest cycle. Light exposure at night mediates these effects, including social misalignment and leads to an inversion of activity and rest, which, in turn, is linked to changes in behaviours. This article reviews the epidemiological evidence on the association between shift work and health, and possible mechanisms underlying this association. First, evidence from findings of the meta-analyses and systematic reviews published in the last 10 yr is presented. In addition, it reports the larger single-occupation studies and recent large population-based studies of the general workforce. Koch's postulates were used to evaluate the evidence related to the development of disease as a result of exposure to shift work. Finally, we discussed limitations of the multiple pathways that link shift work with specific disorders and the methodological challenges facing shift work research. We concluded that the clearest indications of shift work being the cause of a disease are given when there is a substantial body of evidence from high quality field studies showing an association *and* there is good evidence from laboratory studies supporting a causal explanation of the link.

Key words: Shift work, Nonstandard work hours, Health, Circadian system

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Consensus Statements

- 1) There is strong evidence linking shift work and negative health outcomes such as cardiovascular diseases, gastrointestinal and metabolic disorders (type 2 diabetes; metabolic syndrome).
- 2) There is less consistent evidence linking shift work to cancer, mental health problems and reproduction-related problems.
- 3) It is not clear the extent to which the negative health effects of shift work are mediated—either directly and/or indirectly—by circadian misalignment, sleep restriction and social misalignment.
- 4) We need to understand both the mechanisms behind the development of the negative health effects and how countermeasures can be applied under real life conditions.
- 5) Men and women can respond differently to shift work and the risk of developing particular negative health effects may be gender-specific.
- 6) Laboratory findings should be contextualised in the light of ‘real world’ knowledge obtained from field studies.

Consensus statements review expert panel: Thomas KANTERMANN¹ (Chair), John AXELSSON², João Silvestre SILVA³

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Full consensus among panel members on all statements.

Introduction

This manuscript is part of a series of consensus papers developed by the Working Time Society, as commissioned by the International Commission on Occupational Health. The goal of this series is to provide guidance for a broad, international audience of researchers, industry representatives, workers, labor representatives, policy makers, and other stakeholders on managing health risks associated with non-standard working hours. Collectively, the papers provide overviews of the current state of research, identify health and safety risks, make recommendations for effective interventions, and suggest future research directions. Each paper presents a number of consensus statements, developed through the procedures outlined in Wong *et al.*¹⁾, and describes the background information on which the consensus statements are based. The present paper reviews the epidemiological evidence on the association between shift work and health, and possible mechanisms underlying this association.

While non-standard working times are clearly associated with an increased risk of negative health outcomes^{2–5)}, the physiological mechanisms underlying/mediating shiftwork-related disease risk are poorly understood. Several mechanisms have been proposed by which shift work

increases disease risk including circadian misalignment, disturbed sleep, light induced suppression of melatonin levels at night, and reduction in circadian amplitude^{6, 7)}. These factors in turn are thought to disturb a number of physiological and behavioural processes that further contribute to and/or potentiate disease.

The circadian system synchronizes physiology and behaviour to the environment such that the body works as a finely tuned clock. A master clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus coordinates 24-h rhythms in physiology and behaviours throughout the body including other brain regions and peripheral tissues. When aligned or entrained appropriately to the environment, the clock promotes sleep and related ‘anabolic’ functions at night (e.g., immune function and hormone release), and wakefulness and its related catabolic functions during the day (e.g., food intake and metabolism, physical activity)^{5, 8)}. The internal biological day and night are often demarcated by the endogenous melatonin rhythm, which is controlled by the SCN clock^{9, 10)}. In humans, high melatonin levels occur during the biological night and low melatonin levels during the biological day. Circadian alignment occurs when behavioural and physiological processes occur at appropriate biological times and optimise the circadian timing of physiology and behaviour.

On the other hand, circadian misalignment results from a mismatch in internal circadian timing and the environment and/or behaviours/physiology, and is characterised by desynchrony among the timing of internal rhythms^{5, 11)}.

Due to psychosocial, physiological, and work schedule-related factors, some shift workers experience substantial misalignment between the circadian system and the imposed rest/work schedule, while others may show lesser degrees of misalignment. Whether shift workers with greater circadian misalignment are at increased risk for health problems has been hypothesised but is largely unknown. Behaviours associated with shift work may also contribute to internal desynchrony of circadian clocks throughout the body with possible implications for health and disease. For example, findings from non-human animal studies show that the biological clock located in the liver can be desynchronized from the master SCN clock by timed feeding at abnormal biological times—leading to metabolic dysfunction^{12–14)}. Specifically, the liver clock responds most strongly to the timing of food intake whereas the SCN clock responds most strongly to the light-dark cycle. Peripheral clocks can also be synchronized by endogenous temperature cycles¹⁵⁾. Every day behaviours of shift workers that may contribute to internal desynchrony of circadian clocks include light exposure during the dark period, eating at night, being more physically active at night, and sleeping during the day—these factors feed back onto the circadian clock causing desynchronised rhythms and, therefore altered metabolic and body temperature cycles.

Shift work often requires wakefulness to occur at night and sleep to occur during the day. Shift workers obtain less sleep and less refreshing sleep when sleep occurs during the day because the circadian clock is promoting wakefulness, and sleep in shift workers is also often socially curtailed because of family, and work requirements^{16–18)}. Not surprisingly, most shift workers report reduced subjective sleep quality and total sleep time¹⁹⁾. Sleep is most disturbed during rotational and night shift work schedules¹⁹⁾. Early morning shift work can also lead to short sleep as it is difficult to go to bed early due to social requirements (e.g., child care) and to biological drives since the internal clock maximally promotes wake during the early evening²⁰⁾. This, and early wake times, can for many workers result in short and non-refreshing sleep^{4, 21)}. Findings from epidemiological studies suggest that short sleep duration, disturbed sleep, and insomnia symptoms are important factors that are associated with an increased risk of poor health and disease in shift workers²²⁾.

Exposure to light at night (including room light levels that many night shift workers are subject to during their work shifts) can reduce circulating melatonin levels²³⁾. If the light is bright enough, endogenous nocturnal melatonin levels can be completely suppressed. Evidence from studies of cancer in mouse models has suggested, for example, an association between reduced melatonin levels by light at night and increased risk of cancer²⁴⁾.

It is largely unknown how alterations in circadian amplitude may contribute to health and disease in shift workers and therefore additional research is needed to assess the potential physiological role of circadian amplitude in the real world as well as under controlled laboratory conditions. Higher circadian amplitude can provide robustness of the circadian system to perturbation²⁵⁾. Lower circadian amplitude has been hypothesized to contribute to disease (e.g., irregular sleep-wake rhythm disorder, depression)^{26–29)}.

It is possible that the any or all of the mechanisms described above interact to influence health and disease in shift workers. Circadian misalignment, short sleep, reduced melatonin levels, and reduced circadian amplitude may also disturb the health of shift workers by alteration of a number of physiological and behavioural processes that contribute to the development of disease or exacerbate existing disease. These include inflammation, oxidative stress, alterations in the temporal patterns or levels of hormones, reductions in physical activity, and poor dietary habits.

In addition to physiological disruption, changes in shift workers' lifestyle, behaviours and habits play an important role in the impact that work schedules have upon health outcomes. There is some evidence that shift workers are more likely to engage in 'unhealthy' behaviours based on reports of higher incidence of smoking and alcohol intake, together with higher BMI and lower physical activity levels^{5, 30, 31)}. Such behaviours and habits are inexorably linked with work schedules as work schedules inevitably dictate free time (both amount of timing) and thus drive behaviour. For example, working at night dictates sleeping during the day and therefore shifts eating opportunities to the night hours.

It has been suggested that the health consequences of shiftwork appear relatively non-specific and more consistent with what has been labelled as 'lifestyle illness'. That is, shift work may predispose individuals to lifestyle illnesses and that some of the increased health risk for shift workers is due in part to the effects of (mal) adaptive non-circadian lifestyle factors. However, disentangling the relative contribution of circadian and non-circadian

Table 1. Meta-analyses and reviews of the relationship between shift work and health

Authors	Type of article	Number of studies/ participants	Summary findings	Designs
Cardiovascular Heart Disease				
Vyas <i>et al.</i> , 2012	Meta-analysis	34 studies	Shift work associated with myocardial infarction (RR=1.23), ischemic stroke (RR=1.05) and coronary event (RR=1.24); highest risks associated with night work.	Prospective cohort; retrospective cohort; case-control
Frost <i>et al.</i> , 2009	Systematic review	14 studies	Limited epidemiologic evidence of a causal association between shift work and ischemic heart disease.	Retrospective cohort; case-control; nested
Metabolic syndrome				
Wang <i>et al.</i> , 2014	Meta-analysis	13 studies	Dose-response relationship with night work (RR=1.77 with longer exposure); with women at higher risk than men.	Cross-sectional; case-control; prospective cohort; nested
Obesity				
van Drongelen <i>et al.</i> , 2011	Systematic review	8 studies	Crude association between night work and body weight increase; insufficient evidence of confound-adjusted relationship.	Prospective cohort; retrospective cohort
Proper <i>et al.</i> , 2016	Systematic review	11 studies	Shift work associated with body weight gain, risk for overweight and impaired glucose tolerance.	Prospective cohort; retrospective cohort
Type-2 diabetes				
Gan <i>et al.</i> , 2014	Meta-analysis	12 studies	Shift work associated with increased risk (OR=1.09); greater for males (OR=1.37) and rotating shifts.	Prospective cohort; retrospective cohort; cross-sectional
Anothaisintawee <i>et al.</i> , 2016	Meta-analysis	10 studies	Shift work associated with increased risk (RR=1.40).	Prospective cohort; retrospective cohort
Breast Cancer				
He <i>et al.</i> , 2015	Meta-analysis	15 studies	Shift work associated with increased risk (RR=1.12).	Cohort; case-control
Wang <i>et al.</i> , 2013	Meta-analysis	10 studies	Night work associated with increased risk (RR=1.19); dose-response relationship with night work (RR=1.03 for every 5 yr increase of exposure to night work).	Prospective cohort; nested; case-control
Jia <i>et al.</i> , 2013	Meta-analysis	13 studies	Night work associated with increased risk (RR=1.20).	Cohort; case-control
Ijaz <i>et al.</i> , 2013	Meta-analysis	16 studies	Night work associated with increased risk in case-control studies (RR=1.09 for every 5 yr of exposure) but not in cohort studies (RR=1.01).	Prospective cohort; retrospective cohort; nested
Viswanathan <i>et al.</i> , 2009	Meta-analysis	8 studies	Night work associated with increased risk (RR=1.40).	Prospective cohort; case-control
Erren <i>et al.</i> , 2008	Meta-analysis	7 studies	Shift work associated with increased risk (RR=1.40).	Cohort; case-control
Megdal <i>et al.</i> , 2005	Meta-analysis	6 studies	Night work associated with increased risk (RR=1.51).	Prospective cohort; retrospective cohort; nested; case-control
Lin <i>et al.</i> , 2015	Meta-analysis	16 studies	Night work associated with increased risk (RR=1.029 for 5 yr, 1.025 for 5–10 yr, 1.074 for 10–20 yr, and 1.088 for >20-yr).	Prospective cohort
Kamdar <i>et al.</i> , 2013	Meta-analysis	15 studies	Borderline significant association with ever exposed to night work (RR=1.21).	Cohort; case-control
Travis <i>et al.</i> , 2016	Meta-analysis	10 studies	Night work not associated with increased risk.	Prospective cohort

Table 1 continued

Authors	Type of article	Number of studies/ participants	Summary findings	Designs
Other cancer				
Rao <i>et al.</i> , 2015	Meta-analysis	8 studies	Night work associated with increased risk of prostate cancer (RR=1.24).	Cohort; case-control
Wang <i>et al.</i> , 2015	Meta-analysis	6 studies	Night work associated with increased risk of colorectal cancer (OR=1.32).	Cohort; case-control
Reproduction				
Stocker <i>et al.</i> , 2014	Meta-analysis	15 studies	Shift work associated with increased menstrual disruption (OR=1.22). Night work associated with increased risk of early miscarriage (OR=1.29).	Cross-sectional; case-control; prospective cohort; retrospective cohort
Bonde <i>et al.</i> , 2013	Meta-analysis	13 studies	Permanent night work associated with increased risk of miscarriage (RR=1.51).	Cross-sectional; case-control; prospective cohort; retrospective cohort
Palmer <i>et al.</i> , 2013	Meta-analysis	21 studies	Shift work predicted small increase in risk of pre-term delivery (RR=1.04–1.18).	Cross-sectional; case-control; prospective cohort; retrospective cohort
Palmer <i>et al.</i> , 2013	Meta-analysis	11 studies	Shift work not significantly associated with small for gestational age.	Cross-sectional; case-control; prospective cohort; retrospective cohort
van Melick <i>et al.</i> , 2014	Meta-analysis	11 studies	Shift work not associated with pre-term birth.	Cross-sectional; case-control; prospective cohort; retrospective cohort
Gastrointestinal disorders				
Knutsson & Bøggild, 2010	Systematic review	20 studies	Shift work associated with gastrointestinal symptoms and peptic ulcer.	Cross-sectional; cohort.
Depression				
Lee <i>et al.</i> , 2017	Meta-analysis	11 studies	Night shift work associated with increased risk of depression (RR=1.43).	Cross-sectional; longitudinal; prospective cohort.
Angerer <i>et al.</i> , 2017	Systematic review & Meta-analysis	11 studies (5 included in meta-analysis)	Night shift work associated with non-significant increase in risk of depression (RR=1.42).	Prospective cohort.

'Shift work' defined as any pattern of irregular work hours that may or may not involve night work. 'Night work' defined as any pattern of shift work that includes night working. OR: odds ratio; RR: relative risk; HR: hazard ratio. 'Cohort' can be defined as a longitudinal study in which a group of people who share some characteristic is followed through a selected period. It can be retrospective when goes back in time or prospective when requires new data collected ahead.

influences in 'real-world' settings has proved complex, as many field study designs do not permit the statistical separation of maladaptive lifestyle behaviours from the inherent circadian disruption associated with shift work.

In short, the potential effects of shift work on health are probably related to the misalignment between the light-dark cycle and the human activity-rest cycle. Light exposure at night mediates these effects, including social misalignment and leads to an inversion of activity and rest, which, in turn, is linked to changes in behaviours and habits. This complex interaction of biopsychosocial factors leads to an increase in 'at risk' lifestyle behaviours. What is not yet clear is the relative contribution of physiological

and behavioural factors. While this may seem a relatively minor point it is critical with respect to risk mitigation. If the physiological factors are the primary determinants of disease mechanisms, there is probably little we can do to alter these effects short of eliminating shift work. On the other hand, if the effects are mediated primarily through (mal) adaptive changes in behaviour that increase the risk of lifestyle illnesses, these are potentially modifiable through appropriate training and education.

Evidence from Observational Studies

Given the very large numbers of observational stud-

Table 2. Single observational studies of the relationship between shift work and health

Authors	Type of article	Number of studies/ participants	Summary findings
Cardiovascular Heart Disease			
Vetter <i>et al.</i> , 2016	Prospective cohort	N=189,158	Small but significant increase in risk among nurses with prolonged exposure (≥ 10 yr) to rotating night work (HR=1.15).
Breast cancer			
Wegrzyn <i>et al.</i> , 2017	Prospective cohort	N=78,516 & N=114,559	Increased risk associated with ≥ 20 yr exposure to night work, particularly among women exposed during young adulthood (Not significant in first study, women with ≥ 30 yr of shift work, follow-up primarily after retirement. HR=2.15 in second study, younger women with ≥ 20 yr of shift work; HR=1.4 in second study with up-dated exposure information).
Metabolic syndrome			
Guo <i>et al.</i> , 2015	Cross-sectional	N=25,382	Dose-response relationship with night work among women but not men (OR=1.10 for every 10 yr increase in shift work).
Type-2 diabetes			
Silva-Costa <i>et al.</i> , 2015	Cross-sectional	N=14,427	Increased risk associated with >20 yr exposure to night work in both sexes (RR=1.42 for women; 1.06 for men).
Hansen <i>et al.</i> , 2016	Prospective cohort	N=19,873	Increased risk associated with night (OR=1.58) and evening shifts (OR=1.29), but not rotating shifts.
Reproduction			
Gaskins <i>et al.</i> , 2015	Prospective cohort	N=1,739	No association between shift work and fecundity.

'Shift work' defined as any pattern of irregular work hours that may or may not involve night work. 'Night work' defined as any pattern of shift work that includes night working. OR: odds ration; RR: relative risk; HR: hazard ratio.

ies that have examined the links between shift work and health, the first part of this section will focus primarily on the findings of the meta-analyses and systematic reviews published in the last 10 yr (summarized in Table 1). In addition, it will report the larger single-occupation studies (in terms of participants) published since those reviews, within each disease category (summarized in Table 2). The second part of this section will examine recent large population-based studies of the general workforce.

An evaluation was made of each of the meta-analyses and reviews presented here, focussing on their criteria for selecting studies. First, it was assessed whether all of the selected studies in a review found significant associations between shift work and the outcome. Significant findings are more likely to be published than non-significant findings³²⁾ and therefore if a review only includes studies with significant findings, this might suggest that the selection process for the review has not been sufficiently thorough (e.g. has not included searching for unpublished reports). There were no such indications of selection bias in the reviews and meta-analyses described below and thus all were evaluated positively in this regard. Second, each review was assessed in terms of whether it included studies conducted in more than one occupational sector.

This was evaluated as a positive characteristic, as findings based on data from multiple occupations are less likely to be occupation-specific and may therefore be applicable to occupational groups beyond those studied. All of the reviews and meta-analyses described below were evaluated positively in this regard.

Meta-analyses, systematic reviews and selected single-occupation studies

A meta-analysis examining the links between shift work and cardiovascular heart disease (CHD) identified that shift workers have higher risk of myocardial infarction, with the highest risks associated with night work³³⁾. However, an earlier systematic review was equivocal about a causal link, concluding that it was not possible to rule out biases such as inadequate confounder control, selection bias, and misclassification due to very crude measures of night work exposure³⁴⁾. Since these reviews, a large prospective cohort study of female nurses based on the Nurses Health Study (NHS) observed a small but significant increase in risk among nurses with prolonged exposure (≥ 5 yr) to rotating shift work that includes night work³⁾. Uniquely, they also found that cardiovascular risk waned after the cessation of shift work (Table 2).

Turning to the links between shift work and metabolic disorders, a meta-analysis reported a dose-response relationship between night work (number of years exposed) and metabolic syndrome (i.e., the association of visceral obesity, dyslipidemia, abnormal blood pressure, and serum glucose levels in the same individual)³⁵. Female night workers were found to be at higher risk than their male counterparts, which it was suggested might have been due to women being more prone to vitamin D insufficiency. Subsequent to that review, a large study of retired workers found a dose-response relationship between duration of exposure and risk of metabolic syndrome among female but not male night workers (Table 2)³⁶. Two recent systematic reviews considered obesity in shift workers^{37, 38}. Both identified associations between shift/night work and body weight or BMI, but the earlier review³⁸ concluded that there was insufficient evidence of a significant relationship after adjusting for confounders such as age, gender, bodyweight at baseline, and physical activity. Significant confounder-adjusted associations between shift work and type 2 diabetes were demonstrated in two recent meta-analyses^{39, 40}. The earlier review³⁹ found that risk was greater for male shift workers than for females shift workers. Since these two reviews, a large cross-sectional study identified associations between exposure to night work for >20 yr and type 2 diabetes, but in this case with stronger effects in women than in men⁴¹. Another recent large prospective cohort study, which compared risk on different shift patterns worked by nurses, found increased risk of type 2 diabetes associated with night and evening shifts, but not rotating shifts⁴².

The link between shift/night work and breast cancer has been examined by at least 10 meta-analyses to date. Eight of the 10 analyses reported a significant overall association^{43–50}, while another reported an association bordering on significance⁵¹. However, the reviews' authors expressed varying levels of caution regarding the size and reliability of the association, and whether it represented a causal link. The most recent meta-analysis found no significant association between shift work and breast cancer⁵². Since that most recent review, a paper reporting results from two large prospective studies based on the NHS reported that increased risk of breast cancer was primarily associated with long-term exposure to rotating night work during early adulthood⁵³; a finding which may go some way to explaining the lack of association reported by Travis *et al*⁵², as discussed by Schernhammer⁵⁴. Meta-analyses have also identified dose-response relationships between night work and prostate cancer⁵⁵, and between night work

and colorectal cancer⁵⁶.

A meta-analysis of reproductive outcomes reported that shift work was associated with increased menstrual disruption but not infertility, after adjustment for confounders⁵⁷. In addition, night work was associated with increased risk of early miscarriage after adjustment. A meta-analysis of outcomes later in pregnancy observed a marked increase in the risk of miscarriage associated with permanent night work, while the risk for rotating night work was smaller and not significant⁵⁸. Another meta-analysis found that shift work predicted only small increases in risk of pre-term delivery and small-for-gestational-age at birth⁵⁹. A fourth meta-analysis found no association between shift work and risk of pre-term birth⁶⁰. Among the more recent investigations in this area, a prospective cohort study of women trying to get pregnant found no association between shift work (various patterns) and fecundity⁶¹ (Table 2).

Shift workers are more likely than their day working counterparts to report gastrointestinal symptoms and peptic ulcer, according to a systematic review of field studies⁶². However, it is important to note that many of the reviewed studies were cross-sectional and lacked good experimental control of potentially confounding effects.

Two systematic reviews and meta-analyses have recently been published evaluating the links between shift work and depression. The first was a meta-analysis which incorporated the results of 11 studies, 9 of which were cross-sectional, including two conference poster presentations⁶³. They reported that night shift work was associated with an increased risk of depression. They also reported sub-group analyses in which they found that the association was significant among women but not men; and that the association was significant in both studies of nurses (3 studies) and studies of other occupations. They found no link between duration of shift work exposure and risk of depression (based on two studies). Another systematic review that was based exclusively on prospective studies (9 studies identified) was more equivocal in its findings⁶⁴. They found no association among three studies of nurses which examined exposure to night work of up to 2 yr. However, in five studies that drew their samples from the general population, they found evidence of increased risk due to night in at least some sub groups over a long observation period (>4 yr), although with no uniform pattern. Thus one study found an association in women only, while another an association among men working night shifts and women working rotating shifts. Another study found an association in white collar workers but not blue collar workers. A supplementary meta-analysis of five of

the studies found a non-significant trend for increased risk.

Population-based studies

One of the advantages of single-occupation cohort studies over population-based studies of the general workforce is that the former type of study design limits confounding due to differences between occupations (e.g., gender, work environment, shift pattern). However, one of the major limitations of single-occupation cohort studies is that the reported associations between shift work and health may not be applicable to the general population. This section contains a review of recent large population-based studies of the general workforce that have examined associations between shift work and health after adjusting for multiple lifestyle and work-related confounding factors.

Wyse *et al.*⁶⁵ reported a cross-sectional study investigating whether shift work was associated with obesity, diabetes, and well-being in 277,168 working adults who were recruited as part of UK Biobank. Shift work was defined as a work schedule outside usual working hours (i.e., 9am–5pm weekdays). A number of variables were assessed, including body mass index (BMI), body composition, self-reported diabetes and/or cardiovascular disease, immune activation (calculated as the ratio of neutrophils to lymphocytes), neuroticism, and depressed mood. Associations between shift work and body composition, prevalent disease, and mood parameters were investigated using regression models, which were adjusted for a range of lifestyle and work-related confounding factors. Shift workers reported higher BMI, waist circumference, and a higher body fat percentage than non-shift workers. Shift workers were more likely to report diabetes, hypertension and angina, as well as higher immune activation (thought to contribute to the pathophysiology of diabetes) than non-shift workers. Neuroticism scores were higher in shift workers, and shift workers were also more likely to report mood instability, feeling depressed, and lack of enthusiasm, compared with non-shift workers. These findings were independent of multiple confounding factors and suggest that shift work not only compromises metabolic health, but reduces overall well-being.

As noted in the Introduction, one of the proposed pathways linking shift work to chronic disease is behavioural change, or more specifically, a reduction in physical activity (see also ‘*Pathways for health effects among shift workers*’, below). To investigate this issue, Neil-Sztramko *et al.*⁶⁶ used data collected from the Canadian Health Measures Survey, a national cross-sectional survey conducted by Statistics Canada, to compare levels of physical

activity between day workers (self-reported “regular day-time schedule or day shift”) and shift workers (self-reported “regular night shift” or “rotating night shift”). Physical activity data were collected with 4,323 participants using waist-worn accelerometers for seven d. Main outcome variables included the number of min/d where activity occurred at intensities higher than 3.0 metabolic equivalents in bouts of 10 min or more (i.e., moderate-vigorous physical activity) and the number of min/d at intensities less than 1.0 metabolic equivalents (i.e., sedentary time). Mean daily levels of moderate-vigorous physical activity and sedentary time were not different between shift workers and day workers. It is important to note that in this study, overall low levels of physical activity were observed in both day workers and shift workers—with only 15.4% of participants meeting the recommended physical activity guidelines^{66, 67}.

Poor diet is another potential behavioural change that may contribute to the negative health outcomes associated with shift work. Wirth *et al.*⁶⁸ examined the inflammatory potential of diet in a nationally representative sample of 7,643 shift workers and day workers as part of the National Health and Examination Survey, in the United States. Participants were characterised as either shift workers (evening, night, rotating shifts; n=1,445) or day workers (regular daytime; n=6,198). Diet was assessed using a population-based dietary inflammatory index (DII)⁶⁹. The DII, which was developed to characterise an individual’s diet on a continuum from maximally anti-inflammatory to pro-inflammatory, is based on two different sources of dietary intake information (24-h dietary recall and a 7-d dietary recall). Higher DII scores (i.e., more pro-inflammatory) have been associated with impairments in glucose tolerance and circulating inflammatory markers consistent with metabolic syndrome⁶⁸. Participation in any shift work was associated with higher adjusted mean DII values (i.e., more pro-inflammatory) compared to day workers.

Pathways for Health Effects among Shift Workers

Our understanding of the multiple pathways that link shift work with specific disorders is limited for two reasons. First, there are many potential factors that could lead to a disease besides the circadian disruption that is a consequence of inverting day- and night-time activity. Social aspects, inappropriate coping mechanisms, genetic characteristics, type of job, and stress at work are just

some of the factors that may increase shift workers' susceptibility to certain diseases⁷⁰). Second, the term "shift work" has a broad meaning and it is difficult to conceptualise a dose-response relationship. Permanent night work, early morning shift work, alternating shifts, and irregular work hours are among the many types of work schedule that may be deemed as shift work. This makes it difficult to draw reliable conclusions regarding the association between shift work and disease because we do not have an agreed measure of the 'dose' experience by a shiftworker. Thus, for the purposes of this discussion we present some of the most well-known mechanisms for explaining the effects of shift work workers' lives on health and disease risk, regardless of the type of work schedule.

The effects of shift work on circadian misalignment have, for the most part, been examined in simulated shift- and night-work studies focusing on health-related outcomes, using markers of metabolic function, inflammatory responses, and/or cardiovascular measures. Consistently, albeit with some variation, it has been found that these outcomes are altered during 'night shifts' as compared to 'day shifts', during periods of circadian misalignment. With regard to the impact of shift work on sleep, a large body of research, which will not be reviewed here, reports changes in physiological measures associated with sleep restriction in the absence of circadian misalignment (for review see^{4, 71-73}). The effects of shift work on family and community are discussed elsewhere in this special issue (see Arlinghaus *et al.* "Working Time Society Consensus: Evidence-based effects of shift work and non-standard working hours on workers, family and community"). The sleep disturbances reported by shift workers²¹) may be due to circadian misalignment, sleep restriction, or a combination of both. Disturbed sleep may, in turn, be an underlying cause of other symptoms and/or diseases that are prevalent among shift workers, such as inflammatory responses and increased sensitivity to pain, as well as altered metabolism.

Inflammatory responses and pain

Vallieres *et al.*⁷⁴) showed that insomnia contributes to chronic pain, mainly among rotating shift workers. Although the relationship between insomnia and pain is not exclusively seen in shift workers⁷⁵), the sleep restriction and circadian misalignment observed in this population may lead to additional immune/inflammatory changes^{76, 77}). This was supported by evidence from a laboratory study involving chronic sleep disruption and circadian misalignment, in which circadian misalignment

was found to reduce cortisol levels and increase levels of pro- and anti-inflammatory proteins⁷⁸). Given that inflammation plays a role in the development of several chronic diseases associated with shift work, including metabolic syndrome, cardiovascular disease, cancer and diabetes, diets that promote inflammatory responses may represent a target for behavioural interventions to reduce the health impacts of shift work⁶⁸).

Metabolic dysfunction

Metabolic dysfunction (i.e. the failure of bodily process such as the conversion of consumed food into energy) is more prevalent among shift workers^{1, 79-81}), as is one of its main symptoms, namely obesity^{2, 79-81}). Higher levels of obesity may in turn underlie the increased prevalence of obstructive sleep apnea (OSA) that is found among shift workers⁸²). OSA, which is characterised by bouts of interrupted breathing during sleep⁸³), has a well-established association with obesity⁸⁴).

Experimental and observational studies have indicated that circadian disruption and insufficient/poor quality sleep maybe part of the mechanism by which shift work leads to impaired metabolism⁸⁵⁻⁹¹), as summarized in Fig. 1.

Seminal work by Van Cauter and colleagues demonstrated the effect of circadian disruption in glucose and insulin response to meals⁹²). A series of studies followed which examined the impacts of a phase shift on glucose and insulin responses in the laboratory. A 9-h phase advance resulted in significant changes to glucose and insulin responses to a test meal. Using the same protocol, the team also demonstrated changes to lipid metabolism^{93, 94}). These earlier studies were some of the first to point to possible mechanisms by which shift work may impact long-term health, as inappropriate glucose and insulin responses can result, over time, in type 2 diabetes.

In addition to circadian disruption, sleep loss has also been shown to influence metabolic function. For example, a recent study used an 11-d protocol involving three control nights of sleep followed by eight periods of sleep restriction to up to 5 h either during the night hours, or during the day hours. Insulin sensitivity was decreased and inflammation was increased when participants were sleep restricted and these changes were greater when the sleep was scheduled during the day (i.e., sleep loss plus circadian misalignment)⁹¹). Similarly, a circadian misalignment protocol was used to separate the effects of the behavioural rhythm, circadian timing, and circadian disruption on glucose and insulin response to meals⁹⁵). In addition to investigating circadian misalignment by shifting sleep

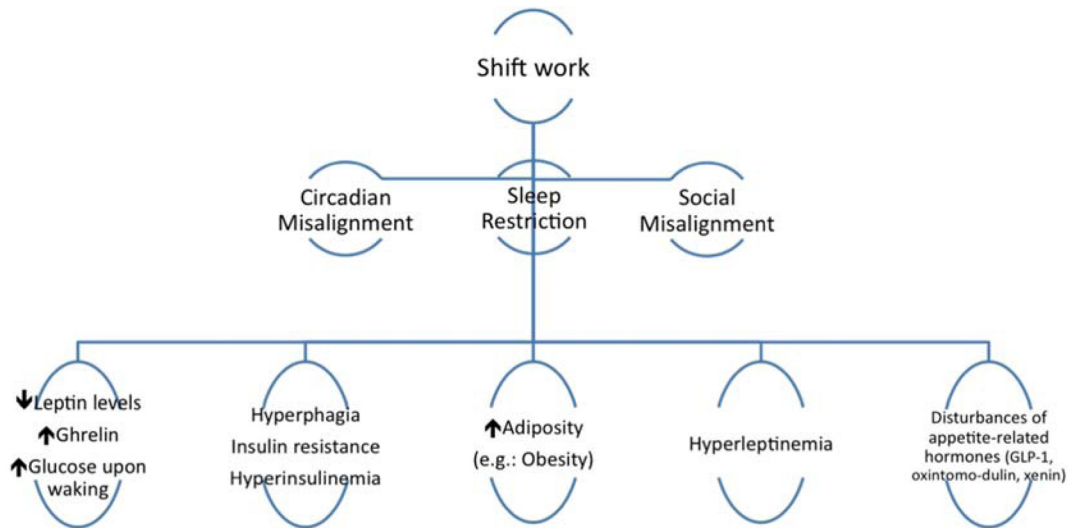


Fig. 1. Mechanisms underlying metabolic dysfunction in shift workers.

to the biological day, meal alignment effects were tested by providing meals at the same point in the behavioural rhythm (breakfast upon waking) but at different points in the circadian rhythm (night sleep breakfast at 0800 h, day sleep breakfast at 2,000 h). Glucose tolerance was reduced following evening meals compared to morning meals (i.e., the circadian effect was independent from the behavioural rhythm). Similarly, glucose response to meals was lower in the misaligned condition, independent of circadian time⁹⁵). Together the findings add to our understanding of the mechanisms by which shift work may increase risk of metabolic disorder and diabetes.

While not ‘simulated shift-work’ per se, forced desynchrony studies also provide vital insights into the potential mechanisms underlying increased disease risk in shift work. The forced desynchrony protocol is an experimental research design that allows the researcher to separate the relative effects of the sleep homeostatic and circadian systems. Using this protocol, Scheer and colleagues reported that circadian misaligned states were associated with decreased leptin (the body’s appetite suppressant) and increased glucose levels, compared to the aligned states. In addition, 3/8 participants in the study reached pre-diabetic states⁸⁷). Moreover, increased glucose response following meals was reported when participants were in a misaligned state in the forced desynchrony protocol⁹⁶) and this study also reported decreased leptin levels with circadian misalignment.

Preferences for certain food types are also reported to change with insufficient sleep^{73, 97}), with participants displaying preferences for high-fat foods following one

night shift⁹⁸). The combination of circadian misalignment and insufficient sleep promote overeating as well as reduced capacity of the body to cope with the food. Thus both the timing of eating and the content of the meals are key factors^{99, 100}). Energy expenditure may also be altered by shift work, with one laboratory study finding that three consecutive simulated night shifts were associated with reduced total daily energy expenditure¹⁰¹). Such effects, in combination with low physical activity levels in shift workers noted previously, could further contribute to weight gain and obesity.

The evidence reviewed above suggests that the increased risk of metabolic dysfunction in shift workers compared with day workers may be linked to dietary pattern, which is often altered in shift workers by the inversion of the sleep-wake cycle. Since shiftworkers can be relatively ‘time poor’, they are more likely to eat easily prepared foods that are of low nutritional quality and that are rich in saturated fats and sugars^{100, 102}). Shift workers also tend to consume lower quantities of healthy foods such as vegetables and fruits^{103, 104}). As well as the potential negative impact on metabolic processes, disrupted eating habits may also underlie the higher prevalence of gastric disturbances among shift workers (e.g. heartburn, abdominal pains, constipation, borborygmus, flatulence); as well as more serious diseases such as chronic gastritis, gastroduodenitis, peptic ulcer, and colitis¹⁰⁵). These problems have been linked to poor eating habits such as binge eating to remain awake at night¹⁰⁰), as well as to the limited availability of healthy foods in the workplace at night. Considering that the circadian temporal system regulates

the appetite¹⁰⁶) as well as the gastric activity (intestinal motility, for example), the nocturnal eating behaviour observed in shift workers can contribute to gastrointestinal disturbances⁶²).

Behavioural countermeasures to the negative effects of shift work and night work on health have been tested in simulated settings. A small study demonstrated beneficial effects on blood pressure during a night shift when participants engaged in moderate exercise immediately prior to the start of the shift. Blood pressure was lower throughout the shift compared to a no exercise condition¹⁰⁷). It remains an open question as to how much additional physical activity shift workers should undertake in order to maintain good health. Preliminary work investigating the effects of fasting during a simulated night shift has shown a reduced glucose response to breakfast as compared to eating during a night shift¹⁰⁸). While the implementation of such countermeasures may have broader ramifications, these findings point towards potential strategies to minimise the negative impacts of shift and night-work on health.

Research showing that shift workers are more likely to engage in unhealthy behaviours is sometimes interpreted in terms of shift workers' adopting inappropriate coping strategies. However, while eating at night may be viewed as an unhealthy behaviour due to circadian misalignment of digestive rhythms, the work pattern requires it. Rather than advocating a simplistic argument that shift workers have poor coping strategies (i.e. blaming the victim), it might be more useful to suggest that there are significant additional risk factors for shift workers (sleep and circadian disruption) which mean that healthy behaviours are even more important for long-term health and well-being. A recent study showed that despite shift workers engaging in levels of physical activity below those recommended for good health, the levels were not substantially different from non-shift workers⁶⁶). Despite the health benefits of physical activity being well known, and central to most public health campaigns, only 15% of people in the study met the levels in the guidelines. All workers engage in 'unhealthy' behaviours and thus the messaging might usefully focus on benefits of health choices rather than the negative consequences. It may be that healthy habits and behaviours are even more important for shift workers but the studies have yet to be designed that can provide such guidance.

Cancer

In 1987, Stevens first proposed a connection between

light exposure at night and breast cancer^{109, 110}). Such a link may have significant implications for night workers who are regularly exposed to artificial light (Fig. 1). As noted above, investigations of the connection between shift work and cancer have produced mixed findings, possibly due to differences between studies with respect to the types of shift being worked, the waveform and intensity of the light, the duration of exposure, and the potentially confounding effects related to concurrent exposure to other possible carcinogens. As also noted above, exposure to artificial light can potentially suppress melatonin, production. Suppressed melatonin production has been linked to reproductive functions of the gonadal pituitary axis and prolactin secretion¹¹¹). This suggests that disturbance of melatonin levels may lead to modulation of the individual's reproductive physiology and subsequent susceptibility to neoplastic growth.

Mental health

Studies of the impact of shift work on mental health have highlighted the potential impact of disturbed social and biological rhythms¹¹²) and decreased exposure to daylight¹¹³). However, there is no clear evidence regarding the mechanisms involved, and there are inconsistencies between the studies¹¹⁴). McClung¹¹⁵) and Richter and colleagues¹¹⁶) pointed out that both circadian misalignment and sleep problems caused by shift work can lead to the development of mood disorders¹¹⁷). These mood effects could, in turn, trigger or exacerbate depressive episodes.

Gender

Gender differences in the effects of shift work have mixed effects, as was seen in some of the systematic reviews and meta-analyses described above. Female shift workers tend to be at greater risk of mortality, disability pension, obesity, fatigue and sleepiness. On the other hand, female shift workers have been found to be at *lower* risk of certain health complaints¹¹⁸). Several factors may contribute to such gender differences. Female shift workers are said to face the 'double burden' of having to cope with demanding work schedules in combination with a higher domestic workload than their male counterparts. The irregular work hours of a rotating shift schedule may be especially disadvantageous for those with childcare responsibilities (i.e. most often women), given the invariant nature of childcare from day to day and week to week. Females may be more likely than men to work highly demanding shift patterns, such as split shifts (i.e. two or

more periods of work within a single day) and ‘quick returns’ (i.e. short intervals between the end of one shift and the start of the next)¹¹⁹. Psychobiological factors may also play a role, with women having been shown to experience more sleep disruption and cognitive impairment in connection with night shifts possibly due to greater sleep disruption¹²⁰.

Methodological issues are likely to underlie the mixed picture that emerges from gender comparisons in the effects of shift work. Most such studies are based on samples from multiple occupational groups. As female and male shift workers tend to work in different occupations, there is a risk that such gender comparisons are confounded by occupational factors.

Overall Evaluation

To evaluate the evidence related to the development of disease as a result of exposure to shift work we have considered Koch’s postulates. Koch’s postulates are a series of basic criteria, first formulated by Robert Koch, for identifying the causative agent of a particular disease. The postulates were originally developed as a method of establishing a causative relationship between a microorganism and a disease, but they have since been adapted and are considered an accepted method for determining cause-effect relationships in the study of human disease¹²¹. The criteria include: strength of association, biologic credibility, consistency with other investigations, time sequence, and dose-response relationship. As a convention, more than one criterion must be met to support a hypothesis that a specific pathogen—in this case shift work—is the cause of the disease; the more criteria that are met, the stronger the evidence for a cause-effect relationship¹²².

Strength of association

The strength of association describes the strength of the relationship between exposure to the proposed cause and symptoms of the disease. Studies examining the relationships between shift work and health typically use odds ratios or risk ratios to provide an indication of the strength of association. Odds ratios are used to compare the relative odds of the occurrence of the outcome of interest (e.g., disease or disorder), given exposure to the variable of interest (e.g., shift work), whereas risk ratios describe the ratio of the probability of an event occurring (e.g., developing a disease) in an exposed group (e.g., shift workers) to the probability of the event occurring in a comparison, non-exposed group (e.g., day workers). Tables 1 and 2

summarise the relative odds and risk ratios for particular diseases as a result of exposure to shift work. In most cases, the odds ratios or risk ratios are greater than one, indicating a strong association between exposure to shift work and the development of various diseases related to health.

Biologic credibility

Several mechanisms have been proposed by which shift work increases disease including circadian misalignment, disturbed sleep, light induced suppression of melatonin levels at night, and reduction in circadian amplitude. Much of our understanding of these proposed mechanisms comes from tightly controlled laboratory studies in which variables are experimentally manipulated (i.e., sleep dose, rest/activity cycle, etc.) and changes in the outcome variables of interest are measured. Laboratory studies involving sleep restriction and/or simulated night/shift work show altered glucose and insulin responses to meals^{87, 93, 96}, alterations in appetite hormones⁸⁷, and changes in preference for particular types of food, as well as reductions in total daily energy expenditure¹⁰¹. Over time, such changes could lead to overweight and obesity, type 2 diabetes, and metabolic syndrome. More recently, changes in gut microbiota as a result of sleep loss and/or circadian misalignment have been proposed as a potential pathway linking shift work to gastro-intestinal dysfunction (for review see¹²²). Field studies are generally supportive of an association between cardiovascular heart disease and shift work; however questions remain regarding the causal nature of that relationship. Laboratory studies indicate alterations in cortisol levels, inflammatory markers, blood pressure and other measures following a period of simulated shift work, all of which may provide potential pathways for the development of cardiovascular disease following exposure to shift work but further replication is required.

The observational evidence linking shift work to reproduction problems and to impaired mental health is somewhat inconsistent, and there is a considerable lack of laboratory studies examining the causal relationship between shift work and the development of these conditions. Perhaps the most hotly debated issue in the arena of shift work and health is the link between shift work exposure and breast cancer. The evidence from field studies is largely supportive of a link, with nine out of ten meta-analyses finding an association, but laboratory studies have yet to provide a conclusive account of an underlying mechanism.

Consistency with other investigations

This criterion refers to a pattern of similar results found by different investigators at different times and in different populations. In Tables 1 and 2, we report the findings from over 300 studies conducted in the last 10 yr that have examined the relationship between health and exposure to shiftwork. These studies have examined shift workers from countries around the world (e.g., Brasil, Denmark, England, Finland, France, Italy, Japan, Sweden, USA, Australia) who are engaged in occupations across a range of industries (e.g., health care, transportation, manufacturing, hospitality). The studies linking shift work and negative health outcomes such as cardiovascular diseases, gastrointestinal, metabolic disorders (e.g., type 2 diabetes, metabolic syndrome) and cancer are consistent, reporting similar patterns of results. There is less consistent evidence linking shift work to mental health problems and reproduction-related problems.

Time sequence

In order for an hypothesized cause-effect relationship between shift work and the development of a particular disease to be supported, exposure to shift work must occur before the development of disease itself. Prospective or longitudinal investigations provide good evidence regarding either the incidence of an outcome or the relative risk of an outcome based on exposure. Tables 1 and 2 identify a number of prospective/longitudinal studies in which individuals are recruited at baseline prior to commencing shift work, and then followed for several years later for incidence of a particular disease. A majority of these studies show clear evidence of temporal sequence; that is, individuals who are disease free prior to shift work exposure are more likely to develop type 2 diabetes, metabolic syndrome, cardiovascular heart disease, mental ill health, and breast cancer following exposure to shift work when compared with individuals who have never been exposed to shift work.

Dose-response relationship

This criterion describes a relationship in which greater exposure to the etiologic agent results in greater risk of contracting the disease. A number of studies reported in Tables 1 and 2 have examined the impact of exposure to shift work (i.e., number of years worked) and the risk of developing disease. The risk of developing metabolic syndrome, type 2 diabetes, and breast cancer increases with increasing exposure to shift to work; with some evidence to suggest prolonged exposure to shift work results in a

small but significant increase in the risk of developing cardiovascular disease. There also appears to be a gender difference in the dose-response relationship between exposure to shift work and development of some diseases, suggesting that some of the health effects of shift work and the proposed mechanisms may be different in men and women.

Methodological Challenges Facing Shift Work Research

A common theme that occurs in several of the reviews cited above is that firm conclusions regarding the link between shift work and impaired health cannot be drawn due to the paucity of reliable evidence from high quality studies. Cross-sectional studies, studies with small and/or unrepresentative samples, and studies that rely on unvalidated self-reported indices can—at best—only be suggestive of a causal link (or an absence of a link) between work schedule and the studied health outcome. Most of the systematic reviews draw upon one or other of the various published sets of criteria for assessing the quality of such studies (e.g. Downs *et al.*¹²³), Wells *et al.*¹²⁴). These highlight the need for longitudinal studies that are based on large representative samples, using reliable and accurate assessments of exposure and outcome, with adjustment for relevant confounders and an appropriate length of follow-up.

Within the reviews of shift work research, one of the most frequently cited methodological weaknesses is the inadequate specification of exposure and the related issue of misclassification (e.g. as ‘shift worker vs. ‘day worker’). At one level, this means failing to adequately account for the number of years of exposure, while at the more ‘acute’ level it means inadequate specification of the shift pattern (both current and in the past). It is widely recognized that the impact of shift work on sleep and circadian rhythms will depend upon the particular shift patterns that are worked e.g. the intensity of night work, the sequence of shifts (presence or absence of rotation, forward or backward rotation, speed of rotation), distribution of rest periods and the days of the week that are worked i.e. just weekdays or including weekends¹²⁵). A related issue is the reliance by many studies on subjective reports of exposure. For example, the self-reported assessment of shift work schedule has been shown to be potentially unreliable when compared to objective work schedule records, increasing the risk that workers are misclassified with respect to their shift work status¹²⁶).

In common with other research fields, a major challenge for shift work researchers is taking adequate account of confounds. Shift workers may be predisposed to poorer health due to pre-existing factors such as (lower) socio-economic status and (poorer) health behaviours, which may confound shift work status even within relatively homogeneous samples^{127, 128}. Other potential confounds/mediators/moderators that should be considered when examining the associations between shift work and health include preference for mornings versus evenings ('chronotype'), neuroticism, extraversion, exposure to light at night, and sleep timing both on work days and non-work days¹²⁹.

The choice of an appropriate control group is crucial. For example, when studying the effects of night work, shift workers are usually compared with day workers, but if the day workers are working shifts themselves (e.g. mornings and evening shifts, which are associated with their own set of challenges for workers' health) then the sensitivity of the comparison may be reduced³⁸.

Another, related, challenge for shift work research is the issue of selection effects and in particular the so-called healthy shift worker effect. This refers to the tendency for individuals with poor health (either as a consequence of shift work exposure, or as a pre-existing condition) to quit shift work (the healthy shift worker survivor effect) or avoid it in the first place (the healthy shift worker hire effect). As a result, the effects of shift work in the general population may be underestimated by research because those who participate in the research are a self-selected/survivor population who are better able than most to tolerate the impact of shift work. Accounting for such effects would ideally involve having detailed and accurate measures of relevant pre-employment factors for both shift workers and the comparison group (usually day workers), together with a prolonged period of follow up.

All of these challenges, along with many other besides, mean that while there is a large and suggestive body of evidence linking shift work with various health complaints, there remains a need for further, well-designed, large scale longitudinal studies to clearly and unambiguously demonstrate those relationships. Some of the reviews cited above argue in favour of prospective cohort studies rather than case-control studies as being the most reliable method of examining these issues (e.g. Ijaz *et al.*⁴⁶), Travis *et al.*⁵²), although others have argued against that view^{130, 131}.

Of course, none of the above is to argue that researchers to date have been in any way negligent. Researchers inevitably have to make compromises in the face of practical

and logistical constraints when collecting data 'in the real world'. The challenge for future research is to build on that past work, identifying and capitalising on those rare opportunities where the constraints are fewer and where the major obstacles can be circumvented.

Final Remarks

Shift work has been associated with a diverse range of significant health problems, from changes in body mass to prostate cancer. The studies reviewed above employed a wide range of methodological approaches, which may account for the disparity in the results obtained. Despite the lack of consistency between studies, a number of broad conclusions can be drawn.

In general, the clearest indications of shift work being the cause of a disease are given when there is a substantial body of evidence from high quality field studies showing an association *and* there is good evidence from laboratory studies supporting a causal explanation of the link.

The differences between shift work schedules, in addition to different occupational categories, may mean that countermeasures will need to be tailored to workplaces. On the other hand, in order to mitigate the effects of shift work on health we need to understand both the mechanisms behind the development of the diseases and how any proposed countermeasures may be applied in real life. We also need to understand the mechanisms that protect some individuals who are exposed to risk factors from developing the associated disease, in order to understand the healthy worker effect. No single methodological approach allows us to do this on its own.

Overall, we can conclude that there is evidence linking shift work and negative health outcomes. It is also clear that life style/behavioural aspects such as diet and physical activity, as well as many other factors, can contribute to the development/prevention of diseases among shift workers.

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