IMPACT OF SHIFTWORK ON DIETARY PATTERNS, HORMONAL CHANGE AND METABOLIC SYNDROME

Baddi Jayalaxmi[1]*, R. Vinoshini[2], Hanumantharaju KN[3], Chaitradeepa G M[4], Chennappa Gurikar[5], Lokesh A C[6]

Abstract

Shift work disrupts the natural circadian rhythm and eating patterns, leading to unfavorable changes in metabolism, insulin resistance, and hormone secretion. In this highly digitalized era, sleep disorders are becoming more common and are associated with an increased burden of chronic disease. Shift workers are at an increased risk for both sleep disorders and metabolic syndrome. This disruption is associated with increased risks of cardiovascular diseases, including hypertension, heart disease, obesity and stroke. The pathways connecting shift work to cardiovascular disease include psychosocial stress, altered work-life balance, sleep disruption, behavioral changes, and physiological stress reactions. Moreover, shift work has been linked to cancer development through mechanisms such as circadian phase shifts, melatonin suppression, sleep disruption, lifestyle factors, and hormonal imbalance. Shift work can impact reproductive health, leading to irregular menstruation, reduced fertility, and problems during pregnancy. Hormonal imbalances, including altered melatonin, leptin, ghrelin, cortisol, and catecholamine levels, play a crucial role in these health effects. Strategies to mitigate shift work-related health problems include maintaining a regular eating pattern, consuming a balanced diet, staying hydrated, avoiding heavy foods at night, limiting junk food and alcohol, and engaging in regular exercise. The disruption of circadian rhythms caused by shift work can have profound effects on metabolism, hormone regulation, and overall health, contributing to chronic degenerative diseases and emphasizing the importance of addressing these challenges in shift work environments. Clinical interventions, including work schedules, light therapy, medications, and dietary habits to improve the circadian synchronicity of shift workers and reduce their risk of morbidity and mortality.

Key words: Shiftwork, dietary patterns, hormonal imbalance, and metabolic syndrome

[1]*Faculty, Department of Food Technology, FLAHS, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India.
[2]Masters in Food Nutrition and Dietetics, Department of Food Technology, FLAHS, Ramaiah University of Applied Sciences - Bangalore, Karnataka, India.
[3]Faculty, Department of Food Technology, FLAHS, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India.
[4]PhD Scholar, Department of Food Technology, FLAHS, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India.
[5]Faculty, Department of Food Technology, FLAHS, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India.
[6]Faculty, Department of Food Technology, FLAHS, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India.

***Corresponding Author: -** Baddi Jayalaxmi
*Faculty, Department of Food Technology, FLAHS, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India.

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1. Introduction

Many of the human body's neuro hormonal cascades, including key metabolic cascades and the sleep-wake cycle, follow 24-hour rhythms. These circadian rhythms evolve in response to a light-dark cycle established by sunrise and sunset along with the daily rhythm of other external factors, such as temperature and noise. Today, people are exposed to synthetic light, heat, and other stimulating cues that do not follow a 24-hour cyclic pattern. These synthetic factors interfere with the carefully coordinated interplay between external regulators and the endogenous maintenance of circadian rhythms (Boivin and Boudreau, 2014). Shift workers are increasingly affected by this phenomenon (McMenamin, 2007). This discordance among shift workers has been linked to disruption in the sleep-wake cycle and metabolic pathways, leading to sleep deprivation and an increased risk of metabolic syndrome (Proper *et al.*, 2016)

Shift work has been around for the most of human history, but it was mainly limited to soldiers and sailors. As shift workers owe it all to Thomas Edison for inventing the light bulb (Edison, 1879). In the late 1800's industrialists soon realized the benefits of shift work. This was quite evident in operations such as steel mills and iron foundries where shutting down and starting repeatedly was expensive and inefficient. Henry Ford in the early 1900's introduced shift work into the auto industry to meet the rising automobile market. During the First and Second World Wars much shift work was utilized to help the war effort. After the Second World War shift work started to rapidly grow in many sectors. Many different kinds of production plants work on a 24 hour bases as well as the food and service industries. It is common place now to find gas stations and grocery stores and hospitals open 24 hours per day. The latest growth industry using shift workers can be seen in the "Call Centre" industry, where information and products ordered can be done anytime of the day or night. 20th century- economic pressures forced companies more workers to shift work. Shiftwork refers to work that is scheduled outside "normal" daylight hours (i.e. 9 am to 5 pm) is called "Shiftwork". Shiftwork is defined as either work at changing hours of the day (eg, morning, afternoon, and night shift) or work at constant but unusual hours of the day (eg, permanent afternoon shift or permanent night shift). The circadian stress refers to the physiological, behavioral, and psychosocial consequences related to the disturbances of the human circadian rhythm (eg the sleep–wakefulness rhythm) (Puttonen*et al.*, 2010). Common shift work professions include production, transportation (mechanics and repairers, construction workers, machine operators, truck drivers, inspectors); technical/ sales/administration (salespersons, retail workers, and administrative support); managerial/ professional (executives, and computer scientists,); other services (healthcare, food, and cleaning); protective services (emergency medical services workers, police, and firefighters).

Shift work has long been associated with negative health outcomes, such as increased risk of cardiovascular disease (CVD) and metabolic diseases, fatigue and sleep disorders, mood disorders, gastrointestinal disorders, and increased risk of miscarriage and premature birth (Moreno *et al.*, 2019; Harrington, 2001). Besides, night shifts are considered "probably carcinogenic to humans", based on limited evidence in humans but stronger evidence in animals by the International Agency for Research on Cancer. Shift work also has an impact on socio-professional outcomes, such as family organization, social activities, increase of errors and accidents at the workplace, or decreased work performance (Ward *et al.*, 2019).

This review aimed to identify highlights regarding some therapeutic implications following the association between night and shift work and metabolic disorders, as well as the mechanisms and pathways responsible for these relationships. Metabolic syndrome, diabetes, obesity and cardiovascular disease are conditions with recent association with night work.

Shiftwork at present: As civilizations progressed, communication and transportation resulted in night mail deliveries, navigation. In production plants like food and service industries started work for 24 hours.20-25% of all workers in developed countries do shift work. The latest growth industry of shift workers is in "Call Centers" and BPO (Business Process and Out sourcing).

Shiftwork is not new. People have worked on shifts through the years in the medical field, transportation, emergency services, the defense, the police force and so on. Factories and mines have also worked on shifts to maximize available resources. What is new is a whole range of industries spawned by globalization, providing services across time zones in a 24/7 economy. The IT (Information Technology) and ITES (Information technology enabled services) industry, in particular, has created the need for ever-increasing numbers of people working on shifts through the day and night. For employees willing to work during the night or other non-traditional hours, there are a large number of job opportunities available. These jobs pay relatively

well and can even benefit those who wish to combine their work with study or family care responsibilities. As a result, huge numbers, especially of young people, are now working on non-traditional shifts.

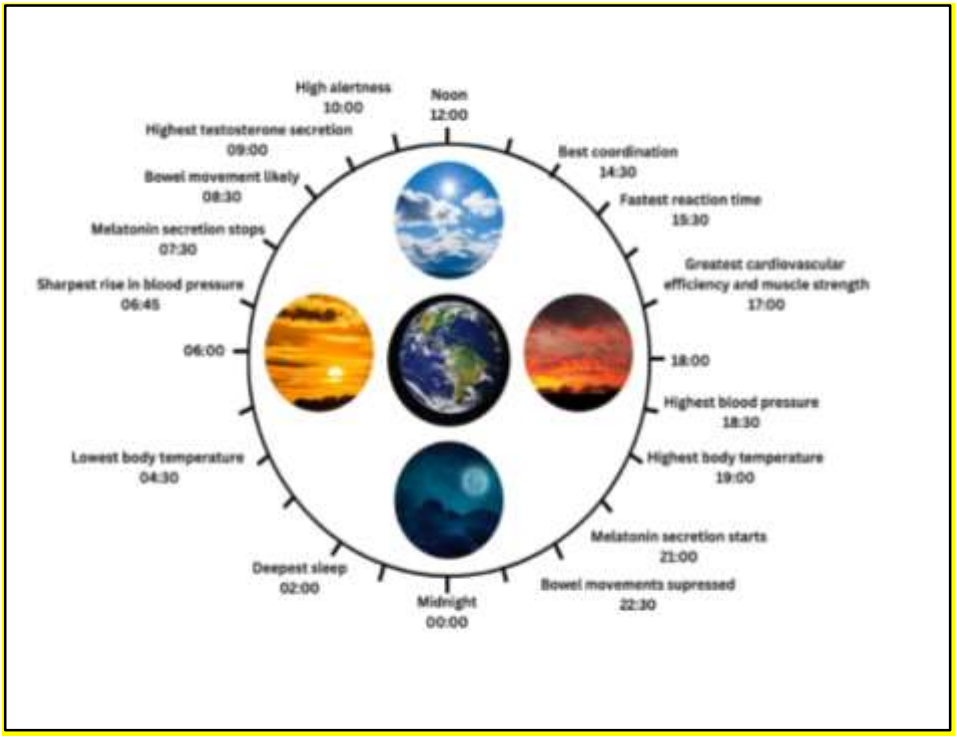

Figure:1 Normal 24 hours Human Circadian clock

2. Shiftwork and its effects on human health: As a result, the work and travel activities disrupt the natural sleep-wakefulness cycle, and result in irregular eating patterns. Many unfavorable alterations in carbohydrate and lipid metabolism causes insulin resistance, growth hormone, corticosteroid secretion patterns change in blood concentrations (Wehrens*et al.*, 2010). Hypertension, coronary heart disease, and myocardial infarction, breast cancer and colon cancer. Alterations in the rhythmicity of the circadian period causes gene –neoplasia.

Shift workers are prone to make more errors when they are tired, especially towards the end of their shift. These can result in serious hazards, especially if they are working on machinery or driving a vehicle, either during their shift or returning home. Shiftwork also disrupts family and social life since the shift worker is out of sync with the routines of family and friends. This often results in relationship issues with spouse, children and even extended family and also tends to isolate the individual from his or her social circle because of non-availability during typical leisure hours.

The severity of clinical problems may have varying magnitudes among individual shift workers. In other words, while some workers tolerate shift work better, others are intolerant (Reinberg *et al.*, 1989). On the basis of intensity of medical complications, it is possible to classify shift workers having good tolerance (with neither complaints nor medical problems), poor tolerance (with medical complaints) and very poor tolerance (severe clinical problems). Clinical intolerance to shift work was defined (Reinberg and Smolensky, 1992) by the existence and intensity of a set of medical complaints: (i) sleep alterations; (ii) persisting fatigue; (iii) changes in behaviour; (iv) digestive troubles and (v) The regular use of sleeping pills. Symptoms (i), (ii) and (v) are present in any intolerant subject. Clinical intolerance to shift work appears to be independent of an individual's age and length of shift working experience. On the contrary, there are some people who believe that aging is associated with a decreased tolerance to shift work, critical age being on an average 40–50 years (Tepas *et al.*, 1993).

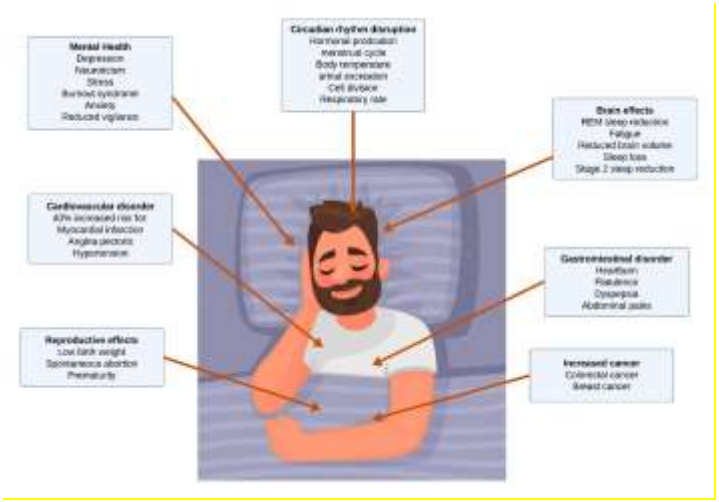

Figure:2 Impact of shiftwork on health

2.1 Sleep quality and length: Shortened or disturbed sleep is among the most common health-related effects of shift work. The effects on sleep length depend on whether the shifts are permanent or rotating, in the latter case the speed and direction of rotation have an impact. In a meta-analytic review, based on 36 primary studies, (Pilcher *et al.*,) concluded that permanent night shifts result in a decrease in the length of sleep (mean 6.6 hours), whereas permanent evening shifts result in an increase (mean 7.6 hours). Furthermore, the shifts within rotating schedules followed the same pattern (mean night 5.9 and evening 8.0 hours), with the addition of morning shifts having a moderate detrimental effect on sleep length (mean 6.6 hours).

Inter-individual differences in tolerance for shift work have been studied primarily in terms of external factors affecting alertness on the job or the ability to rest and sleep while at home. However, there is increasing evidence that neurobiological factors play a role as well, particularly the major processes involved in the regulation of sleep and wakefulness. These include a sleep homeostatic process seeking to balance wakefulness and sleep and a circadian process seeking to promote wakefulness during the day and sleep during the night. Shift work is associated with a temporal misalignment of these two endogenous processes. During nightwork, this misalignment makes it difficult to stay awake during the nightshift and sleep during the day. However, inter-individual variability in the processes involved in sleep/wake regulation is substantial. Recent studies have demonstrated the existence of inter-individual differences in vulnerability to cognitive deficits from sleep loss. Moreover, these inter-individual differences were shown to constitute a trait. Perhaps because of this discrepancy, in operational settings, the inter-individual differences in vulnerability to sleep loss do not appear to be limited due to self-selection mechanisms. Indeed, even among a highly select group of active-duty jet fighter pilots flying a series of simulated night missions, systematic inter-individual differences in performance impairment from sleep loss were still observed. There are significant personal and economic consequences to human error and accidents caused by performance deficits due to sleep loss. It is important, therefore, to study the inter-individual differences in the regulation of sleep and wakefulness in the work environment so that cognitive impairment during shift work may be better anticipated and prevented. Shift work is associated with sleep disruption, impaired quality of life, and is a risk factor for several health conditions. (Van Dongen, 2006).

2.2 Smoking: Shift workers are more likely to smoke than daytime employees; the excess smoking prevalence was between 10% and 40%. As a means of keeping awake during the night shift, smoking should be considered a CVD mediator. When compared to day workers, shift workers had a much higher risk (46%) of beginning to smoke, according to a two-year follow-up research. Smoking is a confounding factor in research on the risk of cardiovascular disease among shift workers. It was found in a research of 239 shift workers and 157 daytime employees that shift work was prospectively associated with increased cigarette consumption, suggesting that smoking may be part of the causal route. Comparing those who typically worked exclusively during the day (74%) to those who typically worked other shifts (26%). No matter their educational background, shift workers are more likely to start smoking. This conclusion may have significant ramifications for investigations into the health effects of shift employment as well as potential interventions meant to lower the

excess health risk among shift employees. The majority of earlier studies compared potential cardiovascular risk variables, such as weight gain and a raised BMI, between night and day workers in a binary manner. Impact of the number of nights worked in the previous year as a predictor on BMI, alcohol intake, smoking behaviours, caffeine use, and exercise habits. (Van Amelsvoort *et al.,* 2006).

2.3 Dietary pattern: The common practises of shift workers, like eating at night and sleeping later than usual, interfere with the synchronisation of the central and peripheral clocks and have an impact on the hormones that are impacted by improper sleep and food timing. poor lipid tolerance and poor glucose regulation, which are risk factors for metabolic disorders, are brought on by the consequent circadian disruption. Dietary patterns provide a way to investigate food and nutrients in conjunction with a disease risk by taking into account the kind, quantity, distribution, and frequency of foods consumed. Night shift employees are said to eat more frequently during the night with shorter fasting intervals, consume more discretionary foods and saturated fat, drink more coffee, and eat fewer vegetables and fruits. The few studies that exclusively examine rotating shift workers as a type of shift schedule and the emphasis on rotating "night" shift energy intakes rather than intakes more representative of changing rotating shift schedules have been limitations. Although the total energy intake of shift workers has previously been reported in systematic reviews as well as meta-analyses to be similar to that of day workers, these reports have been limited by the small number of studies that focus exclusively on rotating shift workers as a type of shift schedule. Individual shift schedules, particularly rotating shift employment, may have an impact on eating habits and energy consumption, but this is less well understood. (Angela B. Clark, *et al*, 2023)

2.4 Weight gain: Shift work can contribute to weight gain due to factors like reduced sleep. People who get less sleep, especially those who sleep for five hours or less, are more likely to become obese. Shift workers are at a 1.14 times higher risk of gaining at least 5% of their body weight compared to those who work during the day. Additionally, individuals working continuous shifts or transitioning from day to night shifts tend to see an increase in their body mass index (approximately 1 kg/m2).

Several studies have examined the differences in the prevalence of cardiovascular risk factors between shift or night workers and day workers. Shift and night workers tend to have a higher prevalence of risk factors such as smoking, dyslipidemia, and weight gain compared to day workers. Night shift workers face unique challenges, including irregular sleeping and eating patterns, which can make it difficult to adhere to traditional weight loss plans. Consuming meals at irregular hours is associated with weight gain, and shift workers often consume high-energy, sugary foods at night, further increasing their risk of gaining weight. (Pietroiusti et al. in 2010).

2.5 Physiological stress and reactions as a pathway: physiological and biological mechanisms that influence the disease process at different phases. We have summed up the results of studies using established independent. The examined mechanisms and risk factors of CVD range from inflammation, blood coagulation, physiological and biological stress mediators (autonomic nervous system and hypothalamic-pituitary-adrenal axis, which control the body's levels of cortisol and catecholamine), and blood pressure to disease conditions such as hypertension and type II diabetes.

There are biological mechanisms underlying the associations observed in the study. Working during the night results in hormonal changes that are correlated to appetite (leptin and ghrelin) (Lowden *et al.,* 2010) and also in lifestyle changes (dietary and physical exercise habits) (Biggi *et al.,* 2008). With regard to hormones, there is a reduction in leptin levels (activation of the sympathetic nervous system due to sleep deprivation) and an increase in ghrelin levels (Spiegel *et al.,* 2004), contributing to increase the appetite and, as a result, the number of meals. Additionally, during NW, gastrointestinal processes related to digestion, to absorption, and to storage are compromised (vagal activity is different during the nocturnal period and secretion of gastric and biliary liquids is minimal at night) (Antunes *et al.,* 2010). Additionally, the reduction in physical activity appears to be related to tiredness caused by work and also to the difficulties that night workers face in participating in types of sporting activities that happen at regular times (Proper *et al.,* 2016).

2.6 Inflammation: Inflammation plays a critical role in the atherosclerotic process, all stages of atheroma formation, and CHD. High sensitive C-reactive protein, leucosyte count, lymphosyte, and NK-cell activity have received some interest in shift work studies. Increased leucocyte counts among rotating shift compared to daytime workers.

Shift work is associated with several negative health effects. The underlying pathophysiological mechanisms are unclear, but low-grade inflammation has been suggested to play a role. Most evidence concerns IL-6 where a recent meta-analysis showed levels to be lower in the morning (Nilsonne *et al.,* 2016). Unfortunately, in the present study most IL-6 data were under the LOD and we could not make any clear conclusions as to whether shift workers suffered from a systemic inflammation with regard to IL-6 or whether there was an alteration seen after a night shift. It was reported that TNF-alpha was not associated with neither sleep disturbances nor sleep duration, whereas IL-6 was associated with sleep disturbance (higher values) but not short sleep duration (Irwin *et al.*, 2016).

Shift workers to have higher levels of inflammatory biomarkers. However, neither work schedule, number of night shifts, number of quick returns, short sleep duration, poor sleep quality, nor having shift work disorder seemed to have a major impact on the levels of a multitude of immunological biomarkers. Yet, levels of IL-1beta and TNF-alpha were higher after a day shift, levels of IL-1beta were higher after a night shift, and levels of MCP-1 were lower both after a day shift and after a night shift, in comparison with morning levels after a night of sleep, respectively, which suggests that work may acutely impact immune function (Bjorvatn *et al.,* 2020).

2.7 Homocysteine and blood coagulation: Plasma homocysteine is an independent risk factor for atherosclerosis and CVD and potentially influences several risk mechanisms of CVD, including endothelial dysfunction, oxidative stress, and atherogenic inflammation. The level of homocysteine was found to be almost twice as high among male shift compared to day workers, while another study reported significantly increased levels only for older shift working men with sleep complaints. The same holds true for microalbuminuria, which is a risk marker for arterial thromboembolism and a predictor of CVD mortality and cardiac events. The association between shift work and albumin excretion, in shift workers may have increased excretion compared to day workers. Similar levels of fibrinogen among day and shift workers, while plasminogen activator and tissue plasminogen activator inhibitor showed lower fluctuations among those working shifts both during the day and night, suggesting some deficiency in the diurnal variation of blood coagulability. Shift work has been shown to increase the risk of cardiovascular disease (CVD) based on several evidences. The classic risk factors of CVD include age, hypertension, smoking, obesity and diabetes. Recently, the serum homocysteine level has been reported to be a valuable indicator of CVD risk. The level of serum homocysteine is known to be a useful indicator of CVD risk and an increase in serum homocysteine level by 5 μmol/mL was shown to increase the CVD risk by 20%–50% in most of the 26 reviewed studies (Humphrey *et al.,* 2008).

Meta-analysis was performed on genetic and prospective cohort studies, an increase in serum homocysteine level by 5 μmol/mL led to a significant increase in CVD risk, but when the level of serum homocysteine was decreased by 3 μmol/mL through the intake of folic acid, for example, the risks of ischemic heart disease, deep vein thrombosis and stroke were predicted to fall by 16%, 25% and 24%, respectively (Wald *et al.,* 2006).

2.8 Cardiac autonomic function: Shift work can have acute effects on the autonomic nervous system, leading to an increase in the activity of the sympathetic nervous system and a decrease in parasympathetic activity both during work and in the sleep period following a shift. This results in reduced regulation of heart rate variability by the parasympathetic system or an elevation in sympathetic activity among those engaged in shift work. Night time employment is specifically linked to a decrease in the sympathetic control of the heart. Shift work may also potentially lead to the prolongation of QT intervals when corrected for heart rate (QTc), indicating a possible inclination towards arrhythmias in individuals working shifts. Additionally, individuals engaged in shift work experience a higher frequency of ventricular extra systoles, and the occurrence of these extra beats correlates with the number of nights worked.

Shift work has been shown to elevate the risk of cardiovascular disease (CVD) based on various lines of evidence. The classic risk factors for CVD, including age, hypertension, smoking, obesity, and diabetes, significantly contribute to this heightened risk. More recently, studies have highlighted that the level of serum homocysteine can serve as a valuable marker indicating an increased risk of developing CVD (Jacob D. Jelmini, et *al*, 2023).

2.9 Cortisol and catecholamine: There is relatively little evidence supporting the hypothesis that cortisol would be directly associated with the development of CVD. However, cortisol and catechol amines may influence stress-induced heart disease. Disturbed cortisol secretion and/or altered timing may influence health risk factors

such as the development of central obesity. Little is known about the relation between shift work and catecholamines. The simulated shift work adrenalin and noradrenalin excretion rates were significantly higher under day compared to night shifts and lower during sleep compared to work. Clear fluctuations in the diurnal pattern of catecholamine excretion during and after night work were observed. Catecholamine secretion shows a distinct circadian variation and the timing of sample collection is critical in shift work studies. Therefore, changes in catecholamine levels may reflect the circadian phase differences, which makes it difficult to interpret the findings in many cases. (Bo-chen Yao, et al, 2019).

2.10 Shift work, work–life balance, and recovery: imbalance and shift work has direct effects on risk factors such as cardiovascular diseases, hypertension and atherogenic lipids. Shift work and irregular working hours can disturb the work–life balance. Even after adjustment for work stress, working in shifts decreases the perceived balance between work and social life. For example, compared to day work, baseline shift work was associated with higher work–home interference over time. shift work may induce psychosocial stress through (i) greater difficulties to control personal working hours, (ii) decreased work–life balance, and (iii) insufficient recovery. Although the basic differences in work stress between day and shift workers may at least partly mediate the association between shift work and the risk of heart disease, shift work also includes specific psychosocial stress factors relevant for CVD.

Behavioral stress as a pathway: Shift work is associated with circadian disruption that also affects behavior. One of the most notable changes can be observed in sleep–wake patterns; from time to time, the main sleep period is temporally displaced and the worker suffers from sleep debt, insomnia, and/or excessive sleepiness. This is most notable in night shifts but also seen in early-morning and late-evening shifts. Other aspects of behavior which may change are smoking, consumption of alcohol, dietary intake, and physical exercise.

The misalignment of circadian rhythms of body functions is responsible of the so-called "jet lag" (or "shift-lag" in this case) syndrome, characterized by feelings of fatigue, sleepiness, insomnia, digestive troubles, irritability, poorer mental agility, and reduced performance efficiency; a person recovers in a few days depending on the length and duration of the phase shift imposed, personal characteristics (e.g. age), and coping strategies. However, it has to be taken into account that the type of shift rotation can significantly affect resting and rising times as well as sleep duration. On the other hand, in the case of continuous shift schedules, it was found that sleepiness decreases passing from a backward- to a forward-rotating shift system, as there are longer rest intervals between shifts (Viitasalo *et al.*, 2008).

2.11 Shift work and cardiovascular disease – pathways from circadian stress to morbidity (Puttonen*et al.*,2010)

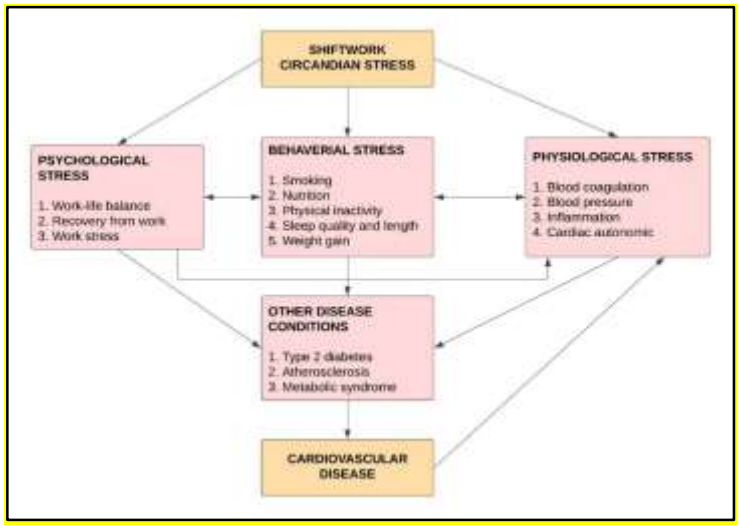

Figure:3 Model for pathways from shift work to cardiovascular disease

There is an evidence that both socioeconomic status and work stress are risk factors for CVD. The exact mechanisms by which shift work causes cardiovascular disease are still not completely understood, but it is thought that the main contributing factors include disturbed circadian rhythms, and confounding factors such as smoking, poor eating habits, and social problems

causing stress which are common among shift workers (Knutsson, 2000).

Psychosocial stress model as a pathway: Three prevalent work stress models, was associated with 50% more compared to non-shift workers. Shift work can act as a specific "circadian" psychosocial stress factor in several ways as mentioned in above model-

First prevalent work stress models, shift work may increase psychosocial stress due to inflexibly organized shifts that leave limited possibilities for employees to influence their working hours.

Second prevalent work stress models, shift work is described as comprising "unsocial" working hours since it may decrease the work–life balance due to possible variability and/or unsocial timing of leisure time.

Third prevalent work stress models, shift work may increase the perception of insufficient recovery from work.

A study in cement plant in Raipur, India investigated the pulmonary function in shift workers. The peak expiratory flow rate (PEFR) was monitored in 202 day workers and 208 shift workers which is one of the measures of pulmonary function. Findings of study indicated that the shift workers (453.9) have consistently lower mean values of PEFR than the day workers (469.8). The results of the present study clearly demonstrated a decreased capacity in shift workers pulmonary function (Chandrawanshi and Pati, 1996). The findings among workers of United States summarized impact of extended work shifts on worker health and safety. The result indicated a decreasing performance and injuries observed while working log hour shifts particularly of 12 Hour. Findings reported that the 9th to 12th hours of work exhibit decreased alertness, increased fatigue, lower cognitive function, increased injuries among workers. The 12-hour night shifts were associated with more fatigue (Caruso, 2004). The links between shift work and the increase in metabolic risk factors for cardiovascular disease (CVD) have been well documented (Ha and Park, 2005). Desynchronisation of circadian clocks, which may occur as a result of shift work, leads to hypertension, dyslipidaemia, insulin resistance and obesity (Staels, 2006).

Shift work changes the diurnal variation of blood pressure from a dipper to a non-dipper pattern (Wolk and Somers, 2007) thus increasing the risk of hypertension among night-shift workers. The normal daily circadian blood pressure rhythm is characterised by a nocturnal fall and diurnal rise. Individuals who show a nocturnal blood pressure (BP) fall of at least 10% of mean arterial pressure (MAP) are classified as dippers (Birkenhäger and Van den Meiracker, 2007). Non-dippers are characterised by a lack of, or a very limited nocturnal BP fall. Cardiovascular outcomes are worsened in individuals who have an excessive morning BP surge and in those who lack the normal nocturnal BP fall.

It has been seen that, among smokers, the number of cigarettes smoked per day increases more in shift workers than in day workers, or that it is much easier for a shift worker to start smoking. Thus smoking may become a mediating, not only a confounding, factor between shift work and CVD (Van Amelsvoort *et al.*, 2006).More recently, some studies have also pointed out the importance of elevated indices of inflammation (in the atherosclerotic process) or other independent risk factors (i.e. omocysteine, fibrinogen) in shift workers as well as changes in autonomic cardiac control, with higher heart rate variability and increased frequency of ventricular extrasystoles (Puttonen *et al.*, 2010).

3.Cardio-Metabolic Consequences of Shiftwork

Energy metabolism is tightly linked with circadian rhythms, exposure to ambient light, sleep/wake, fasting/eating, and rest/activity cycles. External factors, such as shift work, lead to a disruption of these rhythms, often called circadian misalign-ment. Circadian misalignment has an impact on some physiological markers. However, these proxy measurements do not immediately translate into major clinical health outcomes, as shown by later detrimental health effects of shift work and cardio-metabolic disorders.

Short-term circadian misalignment and sleep restriction independently impair physiological processes, including insulin sensitivity, energy expenditure, immune function, blood pressure and cardiac modulation by the autonomous nervous system. If allowed to persist, these acute effects may lead to the development of cardio metabolic diseases in the long term. (Hemmer. A, *et al*, 2021)

3.1 Atherosclerosis: Ultrasonic measures to estimate the level of subclinical atherosclerosis of the carotid intima media. Endothelial dysfunction is an early finding and marker in the development of atherosclerosis. Brachial artery endothelial function was acutely reduced after a 24-hour shift. The greatest decrease in flow-mediated dilation was observed among participants with a longer history of night shift duty. (Ben Tekaya, A., *et al*, 2022)

3.2 Type II diabetes: Shift work predicts a higher incidence of type II diabetes, with an increasing risk as a function of exposure to irregular working hours; also found that obesity may mediate the effect of shift work on diabetes risk. (Wang, L.*et al*, 2023)

3.3 Obesity: The length of time spent on night shift work, how often it's done, and the level of involvement appear to play a role in determining the likelihood of developing overweight or obesity, as indicated by research by Sun et al. In various studies following groups over time, there's a noticeable link between the length of time engaged in shift work and the prevalence of being overweight or obese.

Ramin et al. found a connection between working night shifts and the risk of becoming obese. They proposed that the number of night shifts taking place each month, specifically from 11:00 PM to 7:00 AM, could contribute to obesity risk. However, a different study involving Norwegian nurses did not establish a relationship between the number of night shifts done annually and changes in BMI. The authors of this study raised the possibility of a "survivor effect," meaning that only those who can tolerate night shifts for an extended period would continue this work schedule.

3.4 Metabolic syndrome (MetS): MetS, a risk factor of CVD, is a clustering of cardiac health risk factors such as insulin resistance, hypertension, cholesterol abnormalities, and central obesity.

3.5 Blood pressure and hypertension: Hypertension has been found to be more prevalent among shift compared to day workers or among shift workers only in a certain age group (40–49 years old). A higher risk of incident hypertension among shift workers was evident only in younger participants, while among the older participants a high risk of hypertension was found for those who changed from shift to day work during the follow-up. Furthermore, longer exposure to shift work has been reported to predict the onset of hypertension among males >30 years old. Shift work may exert transient and long-term effects on circadian blood pressure control seen as the change from a "dipping" to "non-dipping" pattern in which the normally observed nocturnal decrease in blood pressure during sleep is impaired. In shift, workers had a smaller drop in the systolic blood pressure during sleep than day workers, and they were more often categorized as "non-dippers". Shift work has also been associated with higher 24-hour blood pressure levels, while the risk of non-dipper status yielded mixed results. The mean systolic blood pressure during a 24-hour measurement has been found to be higher among shift than day workers it entails a high CHD risk. Shift work is also known to increase the risk of gastrointestinal diseases and metabolic disorders. It has been reported that shift workers more frequently experience functional digestive disorders (Lu *et al.,* 2006) with susceptibility to various gastrointestinal diseases, such as digestive ulcers (Zober *et al.,* 1998), gastroesophageal reflux (Li *et al.,* 2008), and it is associated with elevated Body Mass Index (BMI) (Canuto *et al.,* 2013) and overweight (Lowden *et al,* 2010), increased blood glucose level, insulin-resistance, and risk of diabetes (Gan *et al.,* 2015). Many studies have also suggested that shift work increases the risk of cancer development.

4. Hypotheses for mechanisms linking shiftwork and cancer (Fritschi et al., 2011)

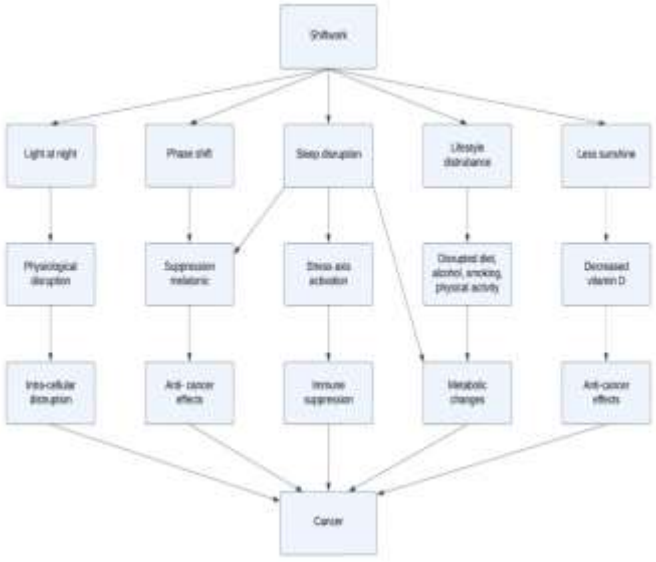

Figure4: Mechanisms between shiftwork and cancer

4.1 Five possible mechanisms by which the proposed link between shiftwork and cancer might act.

- **Phase shift** – animal experiments have reported links between clock gene function and tumor cell induction and growth, and epidemiological studies have shown association between clock gene polymorphisms and some cancers, however, no studies have shown that shift workers have clock gene polymorphism or gene expression linked to cancer.
- **Melatonin suppression –** experiments in animals and in sleep laboratories demonstrate that melatonin is suppressed by light at night. Some support can be found from epidemiological studies, but the results are conflicting, in some studies the study design is not appropriate for measuring cause-effect relationships, and there is little evidence that shiftworkers outside the controlled setting of the laboratory have lower melatonin levels.
- **Sleep disruption** is common in shift workers and there is evidence from animal studies that sleep deprivation can induce cancer, but epidemiological evidence in humans is limited.
- There is some evidence that shift workers are more likely than the general population to engage in lifestyle factors that are known to be associated with increased cancer risk, such as tobacco use, physical inactivity and poor diet.
- In theory shift workers may have lower vitamin D levels because of less opportunity to be outside during daylight, however, the evidence showing that vitamin D is protective against cancer is limited and there are no published studies of sun exposure and vitamin D levels in shift workers.
- Dim light at night workplaces could be used to ensure less suppression of melatonin. Similarly, education on better sleep strategies would increase the quality and quantity of sleep for shift workers; food and exercise regimes could be tailored to the hours worked; and sun exposure at appropriate times could be encouraged.

5. Shift work and Hormonal imbalance

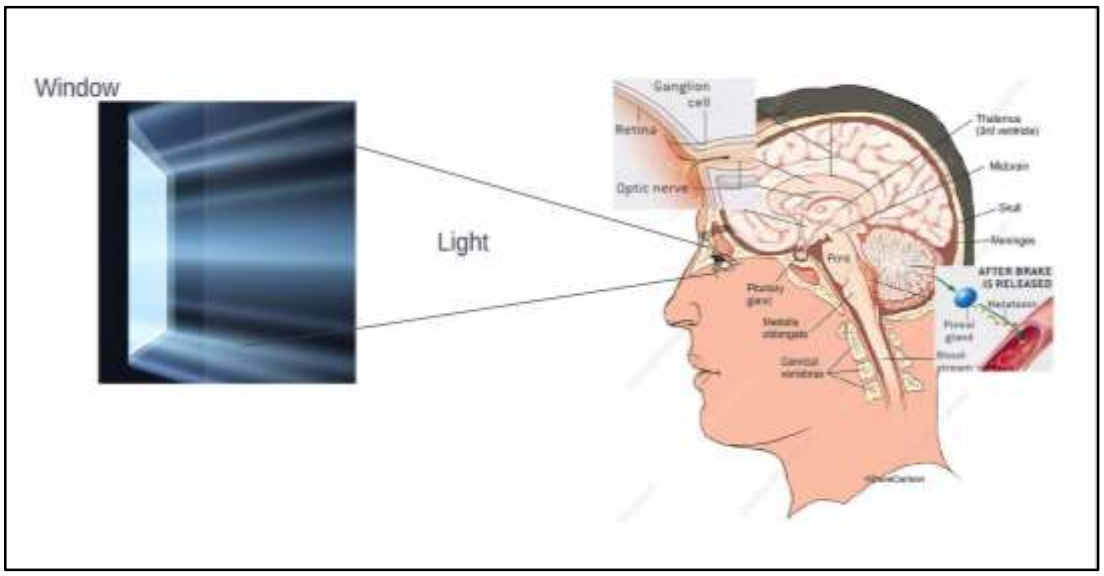

Figure 5: Shift work and Hormonal imbalance

5.1 Light at night suppressing melatonin production- estrogen and cancer

Melatonin is a hormone generated by the pineal gland, and its production follows a daily pattern that varies among individuals, peaking during nighttime when there is no light. Laboratory studies have demonstrated various anti-cancer properties associated with melatonin, including its ability to inhibit tumor formation and reduce levels of reproductive hormones believed to contribute to cancer development. Concerning its role in inhibiting tumor development, there is evidence suggesting that melatonin may impact cell proliferation processes at different levels of organization. Empirically, changes in melatonin release and disruptions in circadian rhythms have been linked to aspects of malignant growth, such as cells triggering their own growth signals, disregarding growth-inhibiting signals, and uncontrolled replication. In animal experiments, multiple studies conducted on rats have shown a decrease in both tumor occurrence and cell proliferation following melatonin administration, encompassing various types of tumors. Furthermore, the removal of the pineal gland (pinealectomy) in rats has been found to increase

the incidence of mammary carcinomas, indicating a potential protective role for melatonin in tumor development. Lastly, both rat hepatomas and human breast cancer xenografts exhibited reduced proliferation when exposed to melatonin-rich blood obtained from healthy premenopausal female volunteers, whereas this effect disappeared when melatonin-depleted blood from volunteers exposed to bright light was used. Collectively, these findings provide evidence supporting the protective role of melatonin in tumor development and proliferation.

Regarding breast cancer, which is linked to long term exposure of breast tissue to estrogen, there has been some interest in the effect of melatonin on reproductive hormones. Melatonin reduces estrogen activity in two ways; indirectly through neuroendocrine mechanisms and directly through actions at the cell level. Melatonin may lead to down-regulation of the neuroendocrine reproductive axis, leading to a reduction of estrogenic hormones that are responsible for the normal and pathological growth of the mammary gland. At the cell level, melatonin oncostatic activity is probably a result of melatonin interactions on the tumor cells estrogen-response pathway. Melatonin may act as a selective estrogen receptor modulator as it interacts with the estrogen-response pathway and counteracts the effects of estrogens. It also can act as a selective estrogen enzyme modulator by regulating the activity of aromatose, the enzyme responsible for the local synthesis of estrogens.

- Release of melatonin is regulated by environmental light levels (blue light-sun) artificial lighting, transmitted to the pineal gland *via*, retina.
- In dark, body produces more melatonin; and production of melatonin drops in light.
- Permanent nightshift, 75% had no adjustment for melatonin rhythm, less than 3% had complete adjustment.
- Regulates other hormones and maintains the body's circadian rhythm. (Arendt J, *et al*, 2022)

5.2 Shiftwork - Leptin and Ghrelin

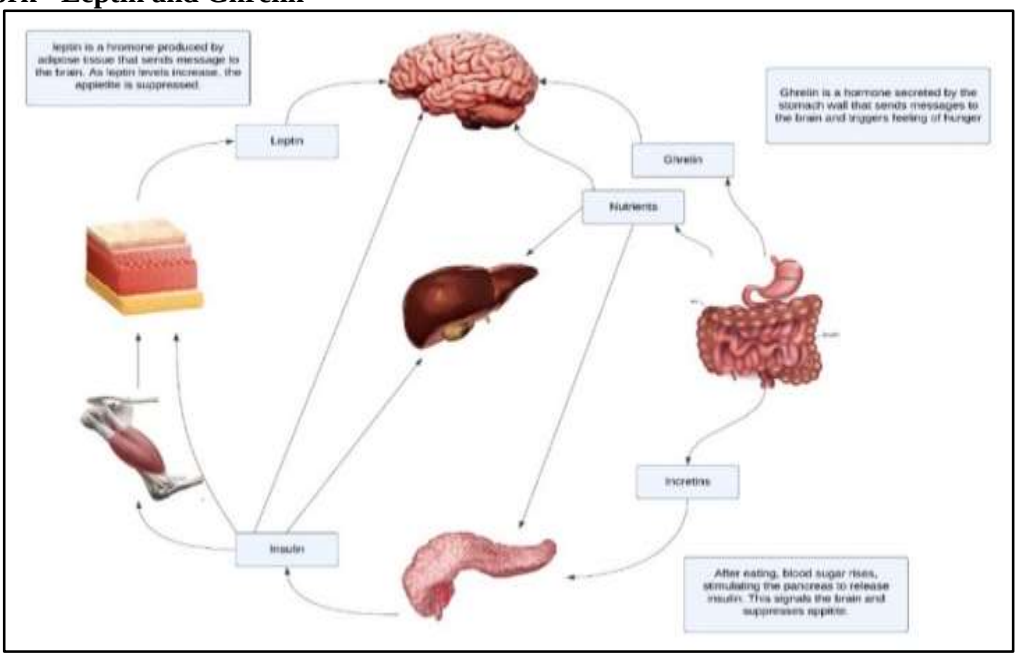

Figure 6: Impact of shiftwork on Leptin and Ghrelin hormone

Leptin and ghrelin are peripheral signals that contribute to central regulation of food intake.

Leptin

- Hormone released by adipocytes, improves glucose and fat metabolism and provides information about energy status to regulatory centers in the brain.
- Circulating leptin are responsive to acute changes in energy balance resulting from increased or decreased caloric intake.
- Shift workers- alteration in nutritional pattern tend to suffer from rhythm misalignment, decreases levels of leptin.

Ghrelin

- Is synthesized - stomach endocrine cells and hypothalamus.
- It stimulates growth hormone secretion and has a potent influence on carbohydrate metabolism via

stimulating glucose levels and inhibiting insulin levels.
- In contrast to the anorexigenic effects of leptin, ghrelin increases food intake, appetite and promotes body weight gain.
- Both peptides (leptin and ghrelin) can be altered by sleep changes (Park, H. K., & Ahima, R. S, 2015).

5.3 Homocysteine and blood coagulation
- Homocysteine levels increases in shift work
- Plasma homocysteine risk factor for atherosclerosis and CVD - endothelial dysfunction, oxidative stress, and atherogenic inflammation.
- Shiftworkers - increased excretion high albumin, fibrinogen and plasminogen activator. (Kang, D., *et al*, 2019).

5.4 Cortisol and catecholamine
- Shift work alter the regulation of cortisol andcatecholamines- stress-induced heart disease, increase in heart rate, blood pressure, blood glucose levels and toxicity to CNS.
- Disturbed cortisol secretion or altered in timing-central obesity (↑LDL and↓ HDL) (Mohd Azmi, N. A. S., *et al*, 2021).

5.5 Shiftwork and Reproductive health: (Culpepper, et al. 2010)
- Increase risk of developing breast cancer, irregular menstruation, reduced fertility, and problems during pregnancy.
- Women working rotating shifts have more difficulty becoming pregnant than night-shift working women.

6. To overcome shiftwork health problems - Diet and Eating Habits
- Maintain a regular eating pattern.
- Eat a balanced diet and drink lots of water.
- Eat main meal according to your work schedule.
- Avoid heavy, greasy foods at night.
- Limit intake of junk food, alcohol, and caffeine.
- Exercise regularly

7. Conclusion: The adverse effects of shift work on health are multifaceted, encompassing cardiovascular diseases, cancer, hormonal imbalances, and reproductive health issues. The disruption of the natural circadian rhythm, altered sleep patterns, and lifestyle changes contribute to these health challenges. The pathways linking shift work to cardiovascular diseases involve psychosocial stress, imbalanced work-life equilibrium, sleep disturbances, behavioral modifications, and physiological stress reactions. Similarly, cancer development is associated with mechanisms such as circadian phase shifts, melatonin suppression, sleep disruption, lifestyle factors, and hormonal imbalances. Hormones like melatonin, leptin, ghrelin, cortisol, and catecholamines play critical roles in mediating these effects.

Strategies to mitigate these health risks among shift workers include maintaining consistent eating patterns, consuming a well-rounded diet, staying hydrated, avoiding heavy meals at night, limiting the intake of unhealthy foods and alcohol, and engaging in regular physical activity. Additionally, interventions such as maintaining controlled light exposure during night shifts and promoting better sleep practices can aid in minimizing circadian disruptions. Recognizing the interconnectedness of these factors underscores the importance of addressing the unique health challenges faced by shift workers and implementing proactive measures to safeguard their well-being.

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