

Review

Shift Work and Health: Current Problems and Preventive Actions

Giovanni COSTA

Department of Occupational Health, University of Milano, IRCCS "Ca'Granda - Ospedale Maggiore Policlinico" Foundation, Milan, Italy

The paper gives an overview of the problems to be tackled nowadays by occupational health with regards to shift work as well as the main guidelines at organizational and medical levels on how to protect workers' health and well-being. Working time organization is becoming a key factor on account of new technologies, market globalization, economic competition, and extension of social services to general populations, all of which involve more and more people in continuous assistance and control of work processes over the 24 hours in a day. The large increase of epidemiological and clinical studies on this issue document the severity of this risk factor on human health and well being, at both social and psychophysical levels, starting from a disruption of biological circadian rhythms and sleep/wake cycle and ending in several psychosomatic troubles and disorders, likely also including cancer, and extending to impairment of performance efficiency as well as family and social life. Appropriate interventions on the organization of shift schedules according to ergonomic criteria and careful health surveillance and social support for shift workers are important preventive and corrective measures that allow people to keep working without significant health impairment.

Key Words: Shiftwork, Nightwork, Occupational health, Work organization, Stress

Introduction

The working time arrangement is a key issue in work organization as it is the basic condition linking human capacities with production means.

This issue has acquired a growing importance in recent decades in relation to the development of new technologies and the extension of basic services to general populations, requiring continuous human assistance and control over the work processes during the 24 hour day. This issue is also associated with the increasing economic competition among companies and countries, due to the progressive globalization of the labour market and productive strategies, which entail an increasingly

intensive and extensive exploitation of productive systems.

The modern "24-hour Society" is the expression of this condition, where we are both consumers and producers at the same time, requiring, on the one hand, the availability of goods and services and, on the other hand, making consumption and production possible at any time of the day and the night [1].

The most recent statistics indicate that the majority of the working population is engaged in irregular or "non-standard" working hours, including shift and night work, week-end work, split shifts, on-call work, compressed weeks, telework, part-time work, variable/flexible working time, and prolonged duty periods (i.e. 12-h shifts); thus, the classical working day, 7-8 a.m. to 5-6 p.m., Monday to Friday, is nowadays a condition affecting a minority of workers, that is 27% of employed and 8% of self employed people according to the 3rd European survey on working conditions [2].

Such diversification of working time should contribute to the improvement of human life (more goods, services, employment, and higher salaries) provided that there are no negative interferences with workers' health and well-being.

Received: October 31, 2010, **Accepted:** November 9, 2010

Correspondence to: Giovanni COSTA

Department of Occupational Health, University of Milan
IRCCS "Ca'Granda - Ospedale Maggiore Policlinico" Foundation
Via San Barnaba 8, Milan 20122, Italy

Tel: +39-02-50320151, **Fax:** +39-02-50320150

E-mail: giovanni.costa@unimi.it

This is not the case in many work situations, and the aim of this paper is to give an overview of the problems to be tackled nowadays by occupational health and some guidelines on how to protect workers' health and well-being.

Circadian Rhythms and Sleep Problems

Shift work, particularly work including night shifts, is the most widely studied condition, as it may interfere at several levels with human homeostasis and well-being.

At the biological level, the perturbation and, sometimes, the inversion of the sleep/wake cycle, connected with the modified activity/rest pattern, is a significant stress for the endogenous regulation of the "circadian" (of about 24 hours) rhythms of biological functions, which are driven by the body clock located in the suprachiasmatic nuclei of the encephalon and synchronised by environmental cues (the light/dark cycle in particular) through non-vision-related photic stimuli from retinal ganglion cells with high sensitivity to light [3-5].

Staying awake at night and trying to sleep during the day is not a physiological condition for diurnal creatures such as humans, who are hence forced to adjust their psycho-physiological state by a phase shift of the daily fluctuation of biological functions, which are normally activated during the day and depressed during the night. This phase shift occurs at a speed of about one hour per day and can widely vary according to the duration and extension of night duties along the shift schedule.

Workers involved in rotating shift work (the large majority) are subjected to a continuous stress to adjust as quickly as possible to the variable duty periods, which is partially and invariably frustrated by the continuous changeovers, whereas permanent night workers may adjust almost completely provided that they continue to maintain their inverted sleep/wake cycle also on their days-off [6].

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.

It is quite obvious that the perturbation of the sleep/wake cycle has its main effect on sleep, that suffers both in quantity and quality according to the timing of shifts and rest periods, the environmental conditions, and the worker's characteristics and behaviours.

After a night shift, workers usually go to bed as soon as

they get home, that is one or two hours after the end of the shift, depending on the commuting time and family commitments (see later for women). This means that they have to sleep during the normal rising phase of biological rhythms, which sustains wakefulness; this makes it difficult to fall asleep and sleep longer. Also, because the environmental conditions are not the most appropriate, such as disturbing noises and lighting, sleep can be further disturbed and wakefulness further extended. Consequently, sleep is reduced by 2-4 h, more frequently or prematurely it is interrupted, and poorer stage 2 and REM (Rapid Eye Movement) sleep is more commonly achieved. The workers perceive this as a less restorative sleep. About one third of shift workers compensate for that by taking a nap in the afternoon, and they also may need to compensate because many workers voluntarily interrupt their sleep around noon to have lunch with other family members. This sleep deficit induces an increased sleepiness during the following night work period, particularly in the second part of it, which is in the early morning, resulting in a higher risk of errors and accidents at work and incidents while traveling home (for example, dozing off at the wheel) [7,8].

Also, in the morning shift, sleep can be notably reduced and disturbed (always with regard to stages 2 and REM affected) due to early awakening, which is not usually compensated by a corresponding advancing of bedtime the night before due to social habits and activities. This early rising time (at 4-5 a.m., when the shift starts at 6 a.m.) induces an increased sleepiness and fatigue during the duty period and for the rest of the day (12) that many shift workers try to compensate for with a nap after returning home. [9,10]. On the other hand, sleep length in the early morning shift increases by about half an hour per each 1-hour delay of the shift start time [11].

On the contrary, the afternoon shift disturbs sleep the least, unless it ends too late (11 or 12 p.m.) or there is a long commuting time that is long enough to significantly delay the retiring time.

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. For example, in the case of the classical semicontinuous shift system with a forward, weekly "5/2" rotation (5 Morning shifts, 2 Rest-days, 5 Afternoon shifts, 2 Rest-days, 5 Night shifts, 2 Rest-days), the interval between two night shifts is always 16 hours, and there are 48 or 56 hours between the last night shift and the following morning or afternoon shift period. On the other hand, in the case of a fast, backward-rotating shift system (1 A, 1 M, 1 N, 2 R), with the morning shift directly after the afternoon shift and the night shift in the same day ("quick return"), the rest intervals between

the shifts last only 8 hours, and the night shift starts in the same day as the morning shift, thus combining the truncation of the sleep preceding the morning shift with its curtailment before the night shift.

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 [12].

Therefore, the combination of circadian disruption and sleep deficit can be responsible for high levels of sleepiness and fatigue during work periods, with consequently higher proneness to performance impairment, thus inducing or favoring errors and accidents.

During a normal day, alertness is high in the morning and early afternoon, being sustained by the circadian activation of biological rhythms and by the restoration given by a normal nocturnal sleep. It progressively decreases during the late afternoon and night hours, and, conversely, sleepiness increases due to the circadian drop of most psychophysical functions and to the prolonging of the time awake. Obviously, it further increases in conditions of repeated and cumulative sleep deprivation, like for several consecutive night shifts [13].

It is not yet clear whether persistent sleep disorders may establish/arise after many years of shift work. This is probably due to the difficulty of following up large groups of shift workers for several years and to the process of self-selection that occurs in the meantime; some retrospective studies (38) seem to suggest a cumulative effect, probably in more vulnerable and older workers.

In recent years, the International Classification of Sleep Disorders has officially defined the Shift Work Sleep Disorder (307.45-1) as one that “consists of symptoms of insomnia or excessive sleepiness that occur as transient phenomena in relation to work schedules” [14]. The disorder may be diagnosed by history and better qualified by polysomnography and by the Multiple Sleep Latency Test, which can also help in the differential diagnosis of other medical or mental sleep disorders, in particular, narcolepsy, sleep apnea syndrome, primitive circadian rhythm (delayed or advanced) sleep disorder, and drug- and alcohol-dependency sleep disorders. It may be defined as “acute” (lasting 7 days or less), “subacute” (more than 7 days but less than 3 months), or “chronic” (3 months or longer) [15].

About 10% of night and rotating shift workers, aged between 18 and 65, have been estimated to have a diagnosable “shift-work sleep disorder” [16].

The key point of the clinical evaluation is the ability to differentiate “tolerable” troubles (compatible with transitory perturbation of the sleep/wake cycle) from more severe or

pathological disorders that require asking for prompt interventions at work (transfer to day work) and personal levels (therapy, rehabilitation). For the latter, the occupational health physician needs the constant help and support from sleep experts for a careful diagnostic process, considering all possible intervening and confounding factors, the most appropriate therapy, and the forensic implications connected with the diagnosis of SWSD as a work-related disease.

Performance Efficiency, Errors, and Accidents

Both homeostatic (time elapsed since prior sleep termination) and circadian (sleep/wake cycle) components interact in determining the extent of the reduction in alertness and psychophysical performance over the waking day, and even more so at night.

Sleepiness, sleep disturbances, chronic fatigue, and oscillatory fluctuations of alertness and vigilance are key factors in causing human errors, and consequent work accidents and injuries, by interacting with organisational factors, such as environmental conditions, job content, workload, and time pressure.

Although it is worth noting that working conditions and risks may change between day and night in relation to fluctuation of work pacing, number of workers on duty, type of tasks (e.g. maintenance works) and supervision, irregular and/or prolonged duty hours are well documented risk factors in many epidemiological studies, even after controlling for other potential confounders.

Some studies that estimated the relative risk of incidents in the morning, afternoon, and night shifts of 8-hour shift systems, in comparable working conditions, showed an increased risk of 18% in the afternoon shift, and of 30% in the night shift, as compared to morning shift. Moreover, other studies reported that the risk increases over successive shifts by about 6% in the second night, 17% in the third night, and 36% in the fourth night [17].

Also the length of hours on duty is a key factor for fatigue-related accidents, as reported by three studies which examined trends in national accident statistics. An aggregated analysis of several studies carried out in English industries [18] showed an almost exponential increase of accidents after the eighth hour of work; this has also been evidenced in Sweden [19], based on examination of the national database of work accidents, and in Germany through the insurance registries on industrial accidents [20]. According to these studies, it is possible to estimate double the risk of accident when working in a 12-h shift

as compared with an 8-h shift. Also, a recent survey of more than 75,000 US workers over a 4-year period [21] confirmed a higher risk of injury strictly related to a progressive increase of working hours and reduction of sleep duration.

However, it is clear that these factors need to be considered in combination with other organizational factors, in particular work load and rest pauses. For example, a 12-h shift, that includes frequent rest pauses and a well balanced work load, can be safer than an 8-hour shift with only one mid-shift break and a high physical and mental load.

Besides industry, the transport sector is particularly sensitive to such problems. Many studies carried out in the last decades have evidenced how drowsiness and fatigue are key risk factors in road and railway accidents of professional drivers [22,23].

Accidents caused by driver fatigue or lapses of attention due to sleep deprivation are often quite severe as the drowsy and/or fatigued driver may not take the appropriate actions to avoid an accident. It was also reported that sleepy drivers often do not perceive their risky condition and frequently drive with closed eyes for 5 to 50 second periods (microsleep) [24-26].

It was found that being sleepy while driving increases the risk of a serious injury crash by eight-fold [27]. Moreover, several studies showed that "single vehicle" accidents on roads have the greatest probability of occurring at night or in the early morning, even when traffic density has been controlled for [28-31]. Similar findings also come from studies on train drivers [32-34].

Härmä et al. [33] recorded severe sleepiness in 50% of the night shifts and in 15-20% of the morning shifts of Finnish train drivers and railway traffic controllers. The risk of severe sleepiness was 6-14 times higher in the night shift and about twice as high in the morning shift as compared with the day shift.

Health Disorders

An increasing amount of epidemiological studies carried out in the last decades show that shift and night work may cause severe long-term effects with regards to health, with a consequent high economic and social cost for both the individual and society.

Psychological and mental health

Shift workers often complain about irritability, nervousness, and anxiety in relation to more stressful working conditions and higher difficulties in family and social life. Persistent disruption of circadian rhythms and sleep deficits may lead to

chronic fatigue, mood disorders, neuroticism, as well as to chronic anxiety and/or depression, creating a situation where workers have higher absenteeism and often require the administration of psychotropic drugs (sedatives and hypnotics) [35-37].

Gastrointestinal disorders

Meal times are important synchronizers of the human life, having both physiological and social aspects. Although shift workers do not significantly modify their total energy intake, they change the timing and frequency (i.e. nibbling) of eating and, sometimes, the content of meals (more fats and carbohydrates in many cases), often being taken cold and during short breaks (snacking).

After sleeping, digestive troubles are most frequently complained about by shift workers (20-75% vs. 10-25% of day workers), due to the troubles being connected with phase displacements between mealtimes and normal circadian phases of gastrointestinal functions (e.g. gastric, bile and pancreatic secretions, enzyme activity, intestinal motility, rate of absorption of nutrients, and hunger and satiety hormones) and to changes in food quality and composition (i.e. more pre-packed food and 'pep' and soft drinks) [38].

Many surveys document that gastrointestinal troubles and diseases are more common in shift workers than in day workers. They can vary from alterations in bowel habits (mainly constipation), difficulties in digestion, flatulence, and pyrosis, to more severe disorders such as gastroduodenitis, peptic ulcer, and irritable bowel syndrome. These disorders were mostly reported in the past by several epidemiological studies, most of which were cross-sectional, and not homogeneous with regards to the diagnostic methods used (i.e. questionnaires, clinical reports, insurance databases, x-ray examination, endoscopy) and controlling for confounders (i.e. smoking, age, socio-economic status) [36,39].

A recent Japanese study on peptic ulcers [40], covering about 12000 workers from several sectors, that combined X-ray and endoscopy showed a double in the relative risk of peptic ulcers in shift workers than in day workers (2.38% vs. 1.03% for gastric ulcer and 1.37% vs. 0.69% for duodenal ulcer).

Moreover, some studies found that the infection by *Helicobacter Pylori* is more prevalent in shift workers than in day workers, which probably is a sign that shift work hampers the natural gastric defence [41,42].

A very recent systematic review of twenty peer reviewed epidemiological studies, reporting an association between shift work and gastrointestinal diseases [43], pointed out that four out of six studies showed a statistically significant association with digestive symptoms, five out of six with peptic ulcers, and

two out of three with functional GI disorders.

Metabolic disorders

Metabolic syndromes (that is abdominal obesity, increased triglycerides, reduced HDL-cholesterol, high blood pressure, increased fasting glucose) are presently one of the most relevant public health risk factors, mainly for their association with type 2 diabetes and cardiovascular diseases [44].

Many studies have recently reported a higher prevalence of nutritional and metabolic disturbances in shift workers, such as overweight and obesity (both general and abdominal), as well as increased triglycerides and total cholesterol (with decreased HDL-cholesterol) blood levels in shift workers engaged in night work, emphasizing its role in the pathogenesis of coronary heart disease [45-51]. This could be due to several factors, in particular the mismatch of circadian rhythms, sleep, and digestive disturbances, changes in daily lifestyle (i.e. quality and timing of meals, nibbling, unbalanced diet), and disturbed socio-temporal patterns, such as work and non-work conflict and related higher stress levels. Also the direction of shift rotation may be relevant: the counter-clockwise shift rotation seems affect, to a greater extent, some metabolic parameters (triglycerides, glucose, and uric acid) than the clockwise rotation.

With regards to the risk of diabetes, some studies reported an impairment of glucose tolerance in shift workers, with increased insulin resistance at night [52,53] and a higher (almost double) prevalence of type 2 diabetes in relation to rotating shift work [54], which appears to increase with years spent doing shift work [55].

The circadian fluctuation of metabolic processes may also influence the efficiency of the detoxification mechanisms (i.e. in the liver) and elimination (i.e. kidney) of chemical substances to which shift workers may be exposed at different times of the day and night. So the risk of intoxication, or excessive retention of harmful substances, may significantly vary according to the different phases of metabolic processes at night, as has been evidenced by the Bhopal disaster (1984), where, surprisingly, thousands of nearby inhabitants died in their sleep, while phase adjusted night workers (and nocturnally active rats) were only marginally affected [56]. This makes clear the need to take into account such aspects also in terms of environmental and biological exposure limits (i.e. TLVs and BEIs) [57].

Cardiovascular disorders

In 1999, Knutsson and Boggild [58] reviewed seventeen studies and concluded that there is evidence in favour of a strong association between shift work and CVD, with shift workers having on average 40% excess risk for ischemic heart disease

as compared to day workers. It has been suggested that the relationship between shift work and CVD is partially due to the combination of the stress connected with an inverted sleep/wake cycle and related circadian disruption with disturbed cardiac autonomic control, sleep deprivation, work/family conflicts, and life style changes [59]. As reported in the previous chapter, several major cardiovascular risk factors, such as smoking, obesity, and dyslipidemia are, in many cases, more prevalent among shift workers than among day workers [60].

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 [61].

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. homocysteine, fibrinogen) in shift workers as well as changes in autonomic cardiac control, with higher heart rate variability and increased frequency of ventricular extrasystoles [62,63].

However it is not always easy to establish a causal relation between shift work and CVD due to many selection biases, besides the well known confounders [64,65]. This is the case of ageing, for example, which is itself a risk factor for CVD but, when combined with shift work, can be underestimated in elderly shift workers due to the "sick shift worker effect", that is workers no longer working on shifts due to intervening health disorders that are more likely to occur with ageing. This was evidenced in a 13-year follow up study on Finnish workers, where the relative risk of ischemic heart disease was higher after 5 years than after 13 years (1.59 vs. 1.34) of shift work [66]. Also, the periodical health surveillance, to which shift workers may be subjected more frequently than day workers, could weaken such associations, as shown by Frost et al. [67] in their review of 16 studies concerning CHD and shift work.

With regards to hypertension, some studies addressed this issue in the last years with mixed and inconclusive results.

Cancer

In 2007, the International Agency on Research on Cancer (IARC) classified "shift work that involves circadian disruption" as "probably carcinogenic to humans" (Group 2A) on the basis of "limited evidence in humans for the carcinogenicity of shift-work that involves night work", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)". This was referring breast cancer in women in particular, on which 9 studies have been published so far, 6 of which were positive, but there are

some other sporadic indications for cancer of the endometrium (1 positive study), prostate (3 studies, 2 positive), colon-rectal (3 studies, 1 positive), and non-Hodgkin lymphoma (1 positive study) [68,69].

The mechanisms by which circadian disruption may favor the induction and/or promotion of malignant tumors are complex and multi-factorial. The multi-level endocrine changes caused by circadian disruption with melatonin suppression via light at night lead to the oncogenic targeting of endocrine responsive breasts in women and possibly the prostate in men. Repeated phase shifting with internal desynchronization may lead to defects in circadian cell cycle regulation, thus favoring uncontrolled growth. Sleep deprivation leads to the suppression of immune surveillance which may permit the establishment and/or growth of malignant clones.

However, the epidemiological studies published so far, although dealing with large cohorts and controlling for several personal confounders, have a rather rough definition of the exposure to shift/night work, which does not allow to properly assess the risk connected with circadian disruption. The information concerning exposure to shift and night work was mainly based either on sporadic self-reported assessment on working shifts, including night (mainly rotating), or on affiliation to a work sector in which shift work involved a somewhat high percentage of workers, according to nationwide databases and registries. Other quantitative and qualitative information on shift schedules (i.e. no. of night shifts per month or year, no. of consecutive night shifts, direction and speed of rotation, length of duty periods) and on possible confounding or mediating factors (concomitant work and personal risk factors) were lacking or quite dis-homogeneous [70].

However, despite these methodological weaknesses, we have to very carefully consider these outcomes as most studies deal with very large cohorts and controlled for several confounders. Taking into account the plausibility of physiopathological mechanisms and the interaction with many other concurrent non occupational risk factors, it is necessary to more precisely analyze the weight of the exposure to irregular working times [71], also with consideration of its social relevance for work and life organization.

Women's reproductive function

The menstrual cycle is the most known monthly ("circatrigintan") hormonal rhythm in humans and it may be disrupted, in association with the circadian rhythms, in rotating shift workers.

A higher incidence of altered menstrual cycle, premenstrual syndrome, and menstrual pains has been reported in

many groups of women shift workers, such as nurses, air crews, and blue collar workers in industry. Some studies also reported a higher incidence of miscarriage and impaired fetal development, including pre-term birth and low birth weight [72].

A large, recent Danish study based on national Registers has found a higher risk of post-term birth in those working on fixed night work as compared with day work (OR = 1.35), a higher risk of full-term low birth weight (OR = 1.80) for fixed evening work, and a slight excess of small babies for their gestational age (OR = 1.09) associated with shift work [73].

A meta-analysis based on 160,988 women in 29 studies designed to evaluate the association of physically demanding work, prolonged standing, long working hours, shift work, and cumulative work fatigue score with preterm birth, showed that, besides the physically demanding work, shift and night work (OR 1.24) were significantly associated with preterm birth [74].

According to some studies, rotating shift work, including night work, has a higher risk of miscarriage than other traditional physical factors (i.e. noise, hot/cold, vibrations, standing work), being second only to lifting heavy loads [75].

Some studies also pointed out that women shift workers have lower fertility and higher abortion rates than their day worker colleagues not only because of the interference on their hormonal rhythms, but also due to a personal choice of avoiding/limiting pregnancies or new babies due to the more complex and difficult organization of their life caused by the conflicts between irregular work schedules and home commitments.

For these reasons, it is worth avoiding night work for pregnant women; in addition, some national legislation states that women are exempt from night work from the beginning of pregnancy as well as the possibility for women to stay in day shifts during the first 2-3 years of age of their children.

Moreover, it may be advisable to transfer those young women who find it difficult to be pregnant to day work in order to give them the possibility to regulate their hormonal cycles.

Social Problems

Shift work also has a relevant interference on family and social life, which may result in psychological stress and psychosomatic disorders [76].

In fact, shift workers can face greater difficulties in combining working and social times as most family and social activities are arranged according to the day-oriented rhythms of the general population. Co-ordination with family timetables may become difficult in relation to the complexity of family (i.e. number and age of children, cohabiting persons), personal

duties (i.e. school, housework), and availability of community services (i.e. shop hours and transports).

Time pressure and work/family conflicts are common problems, particularly for those who have high family burdens or complementary duties (i.e. women with small children), and this may also have a negative influence on marital relationships, parental roles and children's education in addition to the increasing sleep problems, chronic fatigue, and psychosomatic complaints [77-79].

Inter-individual Differences in Tolerance

There is a high inter-individual variability in tolerance to shift work, which can be due to the interaction among individual characteristics, social conditions, and working conditions [80].

Despite several epidemiological studies concerning health troubles and disorders associated with shift and night work, it is not possible to identify some individual characteristics that can be profitably used as predictors of good or scarce tolerance to shift work. Among these characteristics, some authors suggested looking at morningness/eveningness, neuroticism, rigidity/flexibility of sleeping habits, hardiness, and stability of circadian rhythms [81-83].

For example, it is quite well known that “evening” types tolerate better night work than “morning” types; this is connected with the delayed phase position of their circadian rhythms towards evening hours, which partially compensates the fall of biological functions at night. On the other hand, “morning” types cope quite well with early morning shifts (hated by the evening types), thanks to the earlier activation of their biological rhythms. Thus, this characteristic could usefully be taken into consideration to preferably allocate morning and evening types to morning and evening/night shifts, respectively, in the cases of fixed or slowly rotating shift systems, but in the cases of fast rotating shift schedules, which are now the most widely used, both types of workers have problems for opposite reasons.

Moreover, we have to consider that the distribution of these characteristics in the general population is not balanced; the morning type is far more frequent than the evening type, but most are “intermediate” types and thus have problems in any shift.

On the other hand, the characteristics of flexibility of sleeping habits and the ability to overcome drowsiness may help the worker's adaptation to shift work; however, the scarcity of follow-up studies does not allow one, at the moment, to consider it as a predictor of better health conditions in the long-term.

Also, high levels of neuroticisms may be considered as an unfavourable factor for tolerance, but it is not yet clear whether neuroticism is a predictor or an effect of shift work intolerance, due to most of the studies on this topic being cross-sectional.

Besides, good physical fitness increases tolerance by lessening fatigue and improving recovery mechanisms [84].

Certainly ageing may be a key factor of tolerance to shift and night work in relation to the associated physiological and physio-pathological changes occurring during the working life, particularly with regards to sleep length and quality, earlier phasing of circadian rhythms, and higher proneness to circadian desynchronization of biological rhythms [84-86].

With regards to gender, besides the above mentioned negative effects on fertility and pregnancy, a reduced tolerance has been observed in women facing higher work/family conflicts in relation to higher family burden and commitments (i.e. those with small children and/or larger families), which make it more difficult to recover from sleep deprivation and fatigue.

Moreover, less favourable living and social conditions, often reported by surveys in developing countries, and usually associated with poor working conditions and long working hours, may aggravate the impact of shift work on health [87-89].

All these factors may also influence the self-selection process (“healthy worker's effect”) that often occurs among shift workers and may make it difficult to compare different groups, both among shift workers and between shift and day workers.

Health Surveillance and Assessment of Fitness to Work

There are many pathological conditions, either directly associated with shift/night work, as seen above, or independent from it that may be a potential contraindication for shift and/or night work.

They must be carefully evaluated both in terms of severity and possibility of appropriate therapy in the process of assessment of fitness to work, with or without limitations and/or prescriptions, on a temporary or permanent basis [90,91].

This is the case, in particular, for persistent sleep disorders (i.e. chronic insomnia, obstructive sleep apnea syndrome, parasomnias), severe gastrointestinal disorders (i.e. peptic ulcer, chronic hepatitis or pancreatitis, Crohn's disease), cardiovascular diseases (i.e. IHD and severe hypertension), neuro-psychic syndromes (i.e. chronic anxiety and/or depression, seasonal affective disorders, epilepsy), metabolic (i.e. insulin dependent diabetes) and hormonal disorders (i.e. thyroid and suprarenal pathologies), chronic renal impairment, and cancer.

Assessment of fitness to shift work also has to take into

account that: a) shift schedules may be quite different and their effects on health may considerably differ (i.e. continuous or dis-continuous shift systems, slow or fast rotation, clockwise or counter-clockwise rotation, rest days between shifts); b) the consequent effects on health and well-being may be strongly influenced by the coexistence of other occupational risk factors (i.e. work load, environmental conditions, type of task); c) many health disorders may develop in a light form, not able to significantly affect the worker's psycho-physical work ability; d) recent advances in pharmacology and rehabilitation allow one to recover or, at least, to significantly limit the severity and consequences of many health disorders (i.e. in the case of peptic ulcers, hypertension, or IHD); e) several psychosomatic troubles and diseases, ascribable or aggravated by shift work, have a multifactorial etiology, a chronic trend, and are very common in the general population.

Several etiological and/or concausal risk factors may include genetic inheritance, psychological characteristics, life-styles, socio-economic conditions, and other concurrent or pre-existing health disorders. Consequently, intolerance to shift and night work is the result of the interaction among several risk factors dealing with different domains, which can have different weights and relevance among shift workers, both in terms of severity and timing of manifestation during the working life.

Hence, we believe that the above mentioned diseases may be considered from time to time as relative or absolute contraindications to shift and/or night work depending on the specific situation, the type and severity of the disorder, possible interactions with other pathologies and/or to other occupational and non-occupational risk factors, and, above all, with work organization (shift work in particular).

Obviously such disorders are more critical in the case of night work, whereas they may be more compatible with day shifts, except for interferences with sleep (such as in the case of early morning shifts), diet (in the case of metabolic and digestive disorders), and physical work load (in the case of CVD).

For assessment of fitness to work, the OHP has to also carefully consider other conditions able to negatively affect tolerance and health, such as ages over 50, chronic respiratory diseases (i.e. asthma), type 2 diabetes, female hormonal dysfunctions, and current pharmacological therapy (in terms of timing and therapeutic effectiveness, as well as interference of vigilance and sleep).

Medical health checks aimed at assessing the compatibility between health conditions and shift work should be set before starting shift work and at regular intervals afterwards (i.e. every 2-3 years) according to working conditions (type of shift schedules, environmental conditions, work loads) and worker's

characteristics (i.e. age, gender, health, social), with the aim of detecting early signs of mal-adjustment or intolerance.

Health surveillance has to carefully address basic psycho-physiological status (sleep, digestion, women hormonal pattern, body mass index), life styles (i.e. diet, smoking, alcohol and coffee intake, physical activity), previous and current health troubles and disorders (with particular reference to gastrointestinal, cardiovascular, endocrine, metabolic and neuro-psychic), current therapy, and absenteeism due to health impairment.

Clinical checks may be usefully complemented with laboratory and instrumental tests and specialized medical visits aimed at better defining the type and severity of the worker's health conditions, in particular: - polysomnography and/or other sleep and neuro-physiological tests in the case of primary or secondary sleep disorders; - ECG (standard or Holter) and a visit by a cardiologist in the case of IHD or hypertension, and re-admission to work after myocardial infarction; - blood glucose level and glycated hemoglobin to assess the adequate control of diabetes, also performed over a long temporal period; - blood lipids content to assess the proper balance between diet, mealtimes, and metabolic assets; - hormonal levels (i.e. cortisol, melatonin, tiroids), taking into account their circadian rhythms connected with the rest/activity periods because it is important to distinguish between a transitory "masking" effect due to the altered sleep/wake cycle from a more persistent effect due to pathological dysfunction.

Moreover, to better assess the circadian adjustment (or mal-adjustment) of workers complaining of significant health troubles, it may be useful to train them to record their daily sleep and meal times, work and leisure activities, as well as some simple physiological parameters, such as body temperature, heart rate, blood pressure, sleepiness, vigilance, and fatigue, along one or more shift cycles.

Education and Counseling

Both managers and persons in charge with the working time organization, as well as involved workers, must be adequately informed on the possible negative effects of shift work.

The former have to understand which may be the negative consequences of shift work on worker's health and performance, and hence also on productivity, absenteeism, and company costs, in order to plan the best possible countermeasures in terms of work organization and workers management.

The latter have to understand which troubles and disorders are more related to shift and night work and what are the best coping strategies to prevent or limit them, in particular with reference to sleep habits, diet, physical fitness, and leisure

times.

It has been evidenced that good social support from co-workers and supervisors at work, as well as from family members, is able to significantly improve adaptation and tolerance [36,92-94].

Organization of Shift Schedules

It is quite obvious that careful health surveillance has to proceed in parallel with corrective and preventive actions on working time organization, and in particular shift scheduling.

There are thousands of different shift schedules which may have a quite different impact on worker's health and safety, in particular with reference to the amount of night work, timing and duration of shifts, length of shift cycle, speed and rotation of shifts, and position and length of rest days.

Therefore, shift schedules should be designed according to some ergonomic criteria, recognized to be suitable to lessen stress and limit adverse effects on health and well-being by avoiding or minimizing circadian disruption and accumulation of sleep deficits and fatigue, such as: a) limit night work as much as possible; b) avoid a large number of consecutive night shifts; c) prefer quickly rotating (every 1-3 days) shift systems to slowly rotating (i.e. weekly or longer) ones and to permanent night work (also for social reasons); d) prefer clockwise rotation (morning/afternoon/night) to the counterclockwise (afternoon/morning/night) rotation; e) set the length of shifts according to psycho-physical demands; f) avoid morning shifts that start too early; g) set an adequate number of rest days between shifts, particularly after night shifts; h) keep the shift system as regular as possible; i) allow flexible working time arrangements according to worker's needs and preferences [95-98].

However, it should also be taken into account that no one has a priori the best solution, as the arrangement of the shift schedules should be tailored to the specific job demands, personal characteristics, socio-economic conditions, and cultural background of the involved workers. This also requires the workers' participation in the whole process of designing and implementing the shift schedules, not only because of their direct experience of the problems, but also to promote good motivation for adopting the most convenient coping strategies that are able to limit, as much as possible, significant perturbations of their health and social life.

Moreover, further useful countermeasures can be adopted concerning additional rest breaks for meals and naps, supplementary rest-days or holidays to improve recovery, better canteen facilities and social services (i.e. transport, school, and

shop hours), training and rehabilitation courses for shift workers, periodical transfer to day work, and progressive decrease of night work with increasing age [99,100].

Conclusions

Shift and night work interferences on health and well being are complex and multifaceted in their origins and time manifestations, dealing with several aspects of personal characteristics, and working and living conditions.

Referring to the WHO's definition of "health", shift work is a risky condition at all the three reference levels, as it is not only a risk factor for many health disorders (e.g. gastrointestinal, psychoneurotic, cardiovascular, reproductive functions, and probably cancer), but it also perturbs psycho-physical homeostasis (e.g. sleep/wake cycle and circadian rhythms) and hampers family and social life.

Therefore, given that our goal is the preservation of shift workers' health as a whole, it is necessary to go beyond health protection to the view of health promotion. In the former case, our strategies must be oriented to defining the best diagnostic tools for health surveillance and assessing the "risk/benefit" ratio for the worker, and if it is acceptable or not. For the latter, we have to adopt an epidemiological approach, aimed at assessing extension and severity of such a risk factor, and addressing the most appropriate preventive measures at the best "cost/effectiveness" ratio for the workers' groups and the communities in general.

Consequently, it is necessary to apply a systemic approach, dealing with the different domains which in turn can affect the outcomes and address the interventions at their best, involving physio-pathology, psychology, sociology, ergonomics, economics, politics, and ethics.

This implies the concurrent action of several actors beside the occupational health physicians, such as ergonomists, psychologists, sociologists, educators, legislators, as well as managers and workers.

This is the only way to avoid an acritical assessment of mal-adaptation and/or in-tolerance to shift and night work based on sectorial aspects (i.e. some individual characteristics or behaviours) not sufficiently supported by scientific data and longitudinal studies. This can also drive to a risky and even dangerous (i.e. for employment) attitude for selection of shift workers, without taking into consideration the whole context in terms of (shift) work organisation and social conditions, which in many cases are the major intervening factors and are more profitable interventions for subjects, companies, and the whole society.

References

1. Kreitzman L. The 24 hour society. 1st ed. London: Profile Books; 1999. 176 p.
2. Costa G, Akerstedt T, Nachreiner F, Baltieri F, Carvalhais J, Folkard S, et al. Flexible working hours, health, and well-being in Europe: some considerations from a SAL TSA project. *Chronobiol Int* 2004;21:831-44.
3. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature* 2002;418:935-41.
4. Schibler U. Circadian time keeping: the daily ups and downs of genes, cells, and organisms. *Prog Brain Res* 2006;153:271-82.
5. Roenneberg T, Kumar CJ, Mellow M. The human circadian clock entrains to sun time. *Curr Biol* 2007;17:R44-5.
6. Folkard S. Do permanent night workers show circadian adjustment? A review based on the endogenous melatonin rhythm. *Chronobiol Int* 2008;25:215-24.
7. Akerstedt T. Shift work and disturbed sleep/wakefulness. *Occup Med (Lond)* 2003;53:89-94.
8. Akerstedt T, Kecklund G, Knutsson A. Spectral analysis of sleep electroencephalography in rotating three-shift work. *Scand J Work Environ Health* 1991;17:330-6.
9. Akerstedt T, Kecklund G, Selén J. Early morning work-prevalence and relation to sleep/wake problems: a national representative survey. *Chronobiol Int* 2010;27:975-86.
10. Rosa RR. Napping at home and alertness on the job in rotating shift workers. *Sleep* 1993;16:727-35.
11. Ingre M, Kecklund G, Akerstedt T, Söderström M, Kecklund L. Sleep length as a function of morning shift-start time in irregular shift schedules for train drivers: self-rated health and individual differences. *Chronobiol Int* 2008;25:349-58.
12. Viitasalo K, Kuosma E, Laitinen J, Härmä M. Effects of shift rotation and the flexibility of a shift system on daytime alertness and cardiovascular risk factors. *Scand J Work Environ Health* 2008;34:198-205.
13. Sallinen M, Kecklund G. Shift work, sleep, and sleepiness - differences between shift schedules and systems. *Scand J Work Environ Health* 2010;36:121-33.
14. AASM. ICSD 2005. International classification of sleep disorders, revised: diagnostic and coding manual. Darien, IL: American Academy of Sleep Medicine; 2005. 298 p.
15. Sack RL, Auckley D, Auger RR, Carskadon MA, Wright KP Jr, Vitiello MV, et al. American Academy of Sleep Medicine. Circadian rhythm sleep disorders: part I, basic principles, shift work and jet lag disorders. *An American Academy of Sleep Medicine review. Sleep* 2007;30:1460-83.
16. Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. *Sleep* 2004;27:1453-62.
17. Folkard S, Tucker P. Shift work, safety and productivity. *Occup Med (Lond)* 2003;53:95-101.
18. Folkard S. Effects on performance efficiency. In: Colquhoun WP, Costa G, Folkard S, Knauth P, editors. *Shiftwork: problems and solutions*. Frankfurt aM: Peter Lang; 1996. p. 65-87.
19. Åkerstedt T. Work injuries and time of day-national data. *Shift Int News* 1995;12:2.
20. Hänecke K, Tiedemann S, Nachreiner F, Grzech-Sukalo H. Accident risk as a function of hour at work and time of day as determined from accident data and exposure models for the German working population. *Scand J Work Environ Health* 1998;24:43-8.
21. Lombardi DA, Folkard S, Willetts JL, Smith GS. Daily sleep, weekly working hours, and risk of work-related injury: US National Health Interview Survey (2004-2008). *Chronobiol Int* 2010;27:1013-30.
22. Mittleman MM, Carskadon MA, Czeisler CA, Dement WC, Dinges DF, Graeber RC. Catastrophes, sleep, and public policy: consensus report. *Sleep* 1988;11:100-9.
23. Philip P, Akerstedt T. Transport and industrial safety, how are they affected by sleepiness and sleep restriction? *Sleep Med Rev* 2006;10:347-56.
24. Torsvall L, Akerstedt T, Gillander K, Knutsson A. Sleep on the night shift: 24-hour EEG monitoring of spontaneous sleep/wake behavior. *Psychophysiology* 1989;26:352-8.
25. Kecklund G, Akerstedt T. Sleepiness in long distance truck driving: an ambulatory EEG study of night driving. *Ergonomics* 1993;36:1007-17.
26. Horne JA, Reyner LA. Sleep related vehicle accidents. *BMJ* 1995;310:565-7.
27. Connor J, Norton R, Ameratunga S, Robinson E, Civil I, Dunn R, et al. Driver sleepiness and risk of serious injury to car occupants: population based case control study. *BMJ* 2002;324:1125.
28. Pack AI, Pack AM, Rodgman E, Cucchiara A, Dinges DF, Schwab CW. Characteristics of crashes attributed to the driver having fallen asleep. *Accid Anal Prev* 1995;27:769-75.
29. Reyner LA, Horne JA. Falling asleep whilst driving: are drivers aware of prior sleepiness? *Int J Legal Med* 1998;111:120-3.
30. Akerstedt T, Kecklund G, Hörte LG. Night driving, season, and the risk of highway accidents. *Sleep* 2001;24:401-6.
31. Akerstedt T, Kecklund G. Age, gender and early morning highway accidents. *J Sleep Res* 2001;10:105-10.
32. Ingre M, Soderstrom M, Kecklund G, Åkerstedt T, Kecklund L. Train drivers work situation. Working hours, sleep, stress and safety, stress research. Stockholm (Sweden): 2000. Swedish Institute for Psychosocial Medicine; Report no. 292.
33. Härmä M, Sallinen M, Ranta R, Mutanen P, Müller K. The effect of an irregular shift system on sleepiness at work in train drivers and railway traffic controllers. *J Sleep Res* 2002;11:141-51.
34. Lamond N, Darwent D, Dawson D. Train drivers' sleep and alertness during short relay operations. *Appl Ergon* 2005;36:313-8.

35. Cole RJ, Loving RT, Kripke DF. Psychiatric aspects of shift-work. *Occup Med* 1990;5:301-14.
36. Colquhoun WP, Costa G, Folkard S, Knauth P. Shiftwork: problems and solutions. *Arbeitswissenschaft in der betrieblichen praxis*, Band 7. 1st ed. Frankfurt aM: Peter Lang; 1996. 224 p.
37. Nakata A, Haratani T, Takahashi M, Kawakami N, Arito H, Kobayashi F, et al. Association of sickness absence with poor sleep and depressive symptoms in shift workers. *Chronobiol Int* 2004;21:899-912.
38. Lennernäs M, Hambræus L, Åkerstedt T. Nutrient intake in day and shift workers. *Work & Stress* 1994;8:332-42.
39. Knutsson A. Health disorders of shift workers. *Occup Med (Lond)* 2003;53:103-8.
40. Segawa K, Nakazawa S, Tsukamoto Y, Kurita Y, Goto H, Fukui A, et al. Peptic ulcer is prevalent among shift workers. *Dig Dis Sci* 1987;32:449-53.
41. Zober A, Schilling D, Ott MG, Schauwecker P, Riemann JF, Messerer P. Helicobacter pylori infection: prevalence and clinical relevance in a large company. *J Occup Environ Med* 1998;40:586-94.
42. Pietroiusti A, Forlini A, Magrini A, Galante A, Coppeta L, Gemma G, et al. Shift work increases the frequency of duodenal ulcer in H pylori infected workers. *Occup Environ Med* 2006;63:773-5.
43. Knutsson A, Bøggild H. Gastrointestinal disorders among shift workers. *Scand J Work Environ Health* 2010;36:85-95.
44. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365:1415-28.
45. Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. *Occup Environ Med* 2001;58:747-52.
46. Karlsson BH, Knutsson AK, Lindahl BO, Alfredsson LS. Metabolic disturbances in male workers with rotating three-shift work. Results of the WOLF study. *Int Arch Occup Environ Health* 2003;76:424-30.
47. Axelsson J, Lowden A, Kecklund G. Recovery after shift work: Relation to coronary risk factors in women. *Chronobiol Int* 2006;23:1115-24.
48. Biggi N, Consonni D, Galluzzo V, Sogliani M, Costa G. Metabolic syndrome in permanent night workers. *Chronobiol Int* 2008;25:443-54.
49. Lin YC, Hsiao TJ, Chen PC. Persistent rotating shift-work exposure accelerates development of metabolic syndrome among middle-aged female employees: a five-year follow-up. *Chronobiol Int* 2009;26:740-55.
50. De Bacquer D, Van Risseghem M, Clays E, Kittel F, De Backer G, Braeckman L. Rotating shift work and the metabolic syndrome: a prospective study. *Int J Epidemiol* 2009;38:848-54.
51. Lowden A, Moreno C, Holmbäck U, Lennernäs M, Tucker P. Eating and shift work - effects on habits, metabolism and performance. *Scand J Work Environ Health* 2010;36:150-62.
52. Nagaya T, Yoshida H, Takahashi H, Kawai M. Markers of insulin resistance in day and shift workers aged 30-59 years. *Int Arch Occup Environ Health* 2002;75:562-8.
53. Suwazono Y, Dochi M, Oishi M, Tanaka K, Kobayashi E, Sakata K. Shiftwork and impaired glucose metabolism: a 14-year cohort study on 7104 male workers. *Chronobiol Int* 2009;26:926-41.
54. Morikawa Y, Nakagawa H, Miura K, Soyama Y, Ishizaki M, Kido T, et al. Shift work and the risk of diabetes mellitus among Japanese male factory workers. *Scand J Work Environ Health* 2005;31:179-83.
55. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Speizer FE, et al. Prospective study of shift work and risk of coronary heart disease in women. *Circulation* 1995;92:3178-82.
56. Smolensky MH, Reinberg A. Clinical chronobiology: relevance and applications to the practice of occupational medicine. *Occup Med* 1990;5:239-72.
57. Goyal R, Krishnan K, Tardif R, Laparé S, Brodeur J. Assessment of occupational health risk during unusual workshifts: review of the needs and solutions for modifying environmental and biological limit values for volatile organic solvents. *Can J Public Health* 1992;83:109-12.
58. Bøggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. *Scand J Work Environ Health* 1999;25:85-99.
59. Knutsson A, Bøggild H. Shiftwork and cardiovascular disease: review of disease mechanisms. *Rev Environ Health* 2000;15:359-72.
60. Ha M, Park J. Shiftwork and metabolic risk factors of cardiovascular disease. *J Occup Health* 2005;47:89-95.
61. van Amelsvoort LG, Jansen NW, Kant I. Smoking among shift workers: more than a confounding factor. *Chronobiol Int* 2006;23:1105-13.
62. van Amelsvoort LG, Schouten EG, Maan AC, Swenne CA, Kok FJ. Changes in frequency of premature complexes and heart rate variability related to shift work. *Occup Environ Med* 2001;58:678-81.
63. Puttonen S, Härmä M, Hublin C. Shift work and cardiovascular disease - pathways from circadian stress to morbidity. *Scand J Work Environ Health* 2010;36:96-108.
64. Nabe-Nielsen K, Garde AH, Tüchsen F, Hogh A, Diderichsen F. Cardiovascular risk factors and primary selection into shift work. *Scand J Work Environ Health* 2008;34:206-12.
65. Kivimäki M, Virtanen M, Elovainio M, Väänänen A, Keltikangas-Järvinen L, Vahtera J. Prevalent cardiovascular disease, risk factors and selection out of shift work. *Scand J Work Environ Health* 2006;32:204-8.
66. Virkkunen H, Härmä M, Kauppinen T, Tenkanen L. The triad of shift work, occupational noise, and physical workload and risk of coronary heart disease. *Occup Environ Med* 2006;63:378-86.

67. Frost P, Kolstad HA, Bonde JP. Shift work and the risk of ischemic heart disease - a systematic review of the epidemiologic evidence. *Scand J Work Environ Health* 2009;35:163-79.
68. Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol* 2007;8:1065-6.
69. Kolstad HA. Nightshift work and risk of breast cancer and other cancers--a critical review of the epidemiologic evidence. *Scand J Work Environ Health* 2008;34:5-22.
70. Costa G, Haus E, Stevens R. Shift work and cancer - considerations on rationale, mechanisms, and epidemiology. *Scand J Work Environ Health* 2010;36:163-79.
71. Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, et al. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med* 2010.
72. Nurminen T. Shift work and reproductive health. *Scand J Work Environ Health* 1998;24:28-34.
73. Zhu JL, Hjollund NH, Boggild H, Olsen J. Shift work and subfecundity: a causal link or an artefact? *Occup Environ Med* 2003;60:E12.
74. Mozurkewich EL, Luke B, Avni M, Wolf FM. Working conditions and adverse pregnancy outcome: a meta-analysis. *Obstet Gynecol* 2000;95:623-35.
75. McDonald AD, McDonald JC, Armstrong B, Cherry NM, Côté R, Lavoie J, et al. Fetal death and work in pregnancy. *Br J Ind Med* 1988;45:148-57.
76. Colligan MJ, Rosa RR. Shiftwork effects on social and family life. *Occup Med* 1990;5:315-22.
77. Beerman B, Nachreiner F. Working shifts-different effects for women and men? *Work & Stress* 1995;9:289-97.
78. Loudoun RJ, Bohle PL. Work/Non-work conflict and health in shiftwork: relationships with family status and social support. *Int J Occup Environ Health* 1997;3:S71-7.
79. Pisarski A, Lawrence SA, Bohle P, Brook C. Organizational influences on the work life conflict and health of shiftworkers. *Appl Ergon* 2008;39:580-8.
80. Nachreiner F. Individual and social determinants of shiftwork tolerance. *Scand J Work Environ Health* 1998;24:35-42.
81. Costa G. Factors influencing health of workers and tolerance to shift work. *Theor Issues Ergon Sci* 2003;4:263-88.
82. Reinberg A, Ashkenazi I. Internal desynchronization of circadian rhythms and tolerance to shift work. *Chronobiol Int* 2008;25:625-43.
83. Van Dongen HP. Shift work and inter-individual differences in sleep and sleepiness. *Chronobiol Int* 2006;23:1139-47.
84. Härmä M. Ageing, physical fitness and shiftwork tolerance. *Appl Ergon* 1996;27:25-9.
85. Costa G, Di Milia L. Aging and shift work: a complex problem to face. *Chronobiol Int* 2008;25:165-81.
86. Costa G, Sartori S. Ageing, working hours and work ability. *Ergonomics* 2007;50:1914-30.
87. Ong CN, Kogi K. Shiftwork in developing countries: current issues and trends. *Occup Med* 1990;5:417-28.
88. Fischer FM. Shiftworkers in developing countries: health and well-being and supporting measures. *J Hum Ergol (Tokyo)* 2001;30:155-60.
89. Fletcher A. Staying safe in the jungles of borneo: five studies of fatigue and cultural issues in remote mining projects. *Ind Health* 2010;48:406-15.
90. Koller M. Occupational health services for shift and night workers. *Appl Ergon* 1996;27:31-7.
91. Costa G. Guidelines for the medical surveillance of shift workers. *Scand J Work Environ Health* 1998;24:151-5.
92. Kogi K. Improving shift workers' health and tolerance to shift-work: recent advances. *Appl Ergon* 1996;27:5-8.
93. Kogi K. Healthy shiftwork, healthy shiftworks. *J Hum Ergol (Tokyo)* 2001;30:3-8.
94. Pallesen S, Bjorvatn B, Magerøy N, Saksvik IB, Waage S, Moen BE. Measures to counteract the negative effects of night work. *Scand J Work Environ Health* 2010;36:109-20.
95. Knauth P. Designing better shift systems. *Appl Ergon* 1996;27:39-44.
96. Knauth P. Innovative worktime arrangements. *Scand J Work Environ Health* 1998;24:13-7.
97. Gärtner J, Popkin S, Leitner W, Wahl S, Akerstedt T, Folkard S. Analyzing irregular working hours: lessons learned in the development of RAS 1.0--The Representation and Analysis Software. *Chronobiol Int* 2004;21:1025-35.
98. Costa G, Sartori S, Akerstedt T. Influence of flexibility and variability of working hours on health and well-being. *Chronobiol Int* 2006;23:1125-37.
99. Knauth P, Jung D, Bopp W, Gauderer PC, Gissel A. Compensation for unfavorable characteristics of irregular individual shift rotas. *Chronobiol Int* 2006;23:1277-84.
100. Knauth P, Hornberger S. Preventive and compensatory measures for shift workers. *Occup Med (Lond)* 2003;53:109-16.