Inflammation, Sleep, Obesity and Cardiovascular Disease

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Abstract: Evidence is emerging that disturbances in sleep and sleep disorders play a role in the morbidity of chronic conditions. However, the relationship between sleep processes, disease development, disease progression and disease management is often unclear or understudied.

Numerous common medical conditions can have an affect on sleep. For example, diabetes or inflammatory conditions such as arthritis can lead to poor sleep quality and induce symptoms of excessive daytime sleepiness and fatigue. It has also been suggested that poor sleep may lead to the development of cardiovascular disease for which an underlying inflammatory component has been proposed. It is therefore important that the development and progression of such disease states are studied to determine whether the sleep effect merely reflects disease progression or whether it may be in some way causally related. Sleep loss can also have consequences on safety related behaviours both for the individuals and for the society, for example the increased risk of accidents when driving while drowsy. Sleep is a complex phenotype and as such it is possible that there are numerous genes which may each have a number of effects that control an individual's sleep pattern.

This review examines the interaction between sleep (both quantity and quality) and parameters of cardiovascular risk. We also explore the hypothesis that inflammation plays an essential role in cardiovascular disease and that a lack of sleep may play a key role in this inflammatory process.

Aim: To review current evidence regarding the endocrine, metabolic, cardiovascular and immune functions and their interactions with regard to sleep, given the current evidence that sleep disturbances may affect each of these areas.

Keywords: Sleep, obesity, cardiovascular disease, inflammation, innate immunity.

INTRODUCTION

Sleep is a natural process and yet the exact purpose of sleep and its effect on health and disease remains to be fully elucidated. Both physiological and pathological sleep is divided into two states: non-rapid-eye-movement (NREM) sleep and rapid-eye movement (REM) sleep [1]. It has been suggested that it is crucial for the maintenance and restoration of homeostasis through the regulation of energy, repair and infection control and that it may be important in the programming of the brain [1-3]. It is now particularly relevant to understand the importance of sleep, as sleeping habits within our society have been changing over a period of years as a result of decreased dependency on daylight hours, increased shift-work and changes in lifestyle and home environments [4, 5]. Statistics from the National Sleep Foundation in America suggest that approximately one-third of Americans sleep 6.5 h a night or less Fig. (1) [5].

It is well established that sleep disorders such as sleep apnoea can lead to serious health problems including cardiovascular disease [6-9]. New data suggests that ‘healthy’ individuals who do not get enough sleep might be at risk of poor health in the future [10, 11]. Moreover, there is increasing evidence to suggest that sleep disturbances may be an impor-
which is reduced following successful treatment with Continuous Positive Airway Pressure (CPAP), surgery (uvulopalatopharyngoplasty (UPPP)) or oral appliance [15]. Within the general population sleep complaints are very common and are often associated with medical, psychological and social disturbances [16]. Inflammatory processes are important in the development and progression of cardiovascular disease and it is possible that disturbances in sleep patterns may affect these processes Fig. (2).

Fig. (2). Sleep loss, inflammation and cardiovascular disease

Patients with obstructive sleep apnea (OSA) syndrome who have associated cardiovascular disease have significantly elevated C-reactive protein (CRP) compared to those with OSA syndrome but without cardiovascular disease (CVD) or those without OSA syndrome or CVD [12].

Age, Sleep and Inflammation

Age is a risk factor for cardiovascular disease and ageing and is associated with changes in length and quality of sleep as well as an increase in the prevalence of sleep complaints [13]. Sleep problems increase with age and the developed world is experiencing an increase in its ageing population. Likewise, the number of individuals with chronic illnesses is increasing. It is therefore important that the bidirectional effect of sleep on disease progression and development is evaluated. Furthermore, it has been demonstrated in young adults that sleep deprivation leads to metabolic, systemic and immune changes that are similar to those observed in ageing and age-related disorders [13]. However, although healthy elderly adults spend more time in bed, they spend less time asleep and are more easily aroused from sleep than younger individuals [17]. Ageing is associated with an increase in Sleep-Disordered Breathing (SDB), daytime sleepiness and insomnia as well as loud snoring, difficulties maintaining sleep, fatigue, mood effects and impairment of daily activities. These factors can lead to an increase in depression, memory problems, a decline in cognitive functioning and a lower quality of life [18, 19, 20].

The ageing process is associated with changes in the metabolic process and disease development and evidence is accumulating to suggest that sleep-deprivation is associated with similar changes. Furthermore, there is an increasing body of evidence to suggest that the ageing process, sleep and the inflammatory processes are related [21-24]. It is important that not only are sleep regulatory mechanisms studied but the effect of ageing on these processes are determined. A better understanding of the boundaries between normal and abnormal age-related changes in sleep behaviour should allow the development of intervention guidelines. Moreover, the exact nature of relationships and causality between sleep, age and inflammation remain to be elucidated. Increased levels of a number of inflammatory markers in elderly population have been observed, for example CRP and interleukin -6 (IL-6) increase with age [21, 22]. Furthermore, partial short term sleep deprivation gives rise to a similar pattern of CRP response [23]. Sleep deprivation is also associated with an increased gene expression of heat-shock protein [24]. It is therefore possible that sleep deprivation may contribute to the increased systemic inflammation observed in ageing. The exact process however remains to be determined but may also involve oxidative stress [25] or the regulation of growth hormone [26] and its associated effect on the immune function.

Gender, Sleep and Inflammation

Men are at increased risk of CVD but it is not clear whether this is associated with gender differences in patterns of sleep. It has also been suggested that the menopause also may be a risk for sleep disordered breathing (SDB) [27]. Gender differences in inflammatory markers have been observed [28]. We have shown that certain adhesion molecule levels are lower in women than in men [28]. Furthermore, it is possible that the association between sleep and cardiovascular risk factors such as the Body-Mass-Index (BMI) may vary between sexes, at least in adolescents. Knutson demonstrated that while short sleep may have an effect on BMI in young men this does not appear to be the case in young women [29].

Ethnicity, Sleep and Inflammation

South Asians have a higher risk of CVD than whites and individuals of African origin appear to be protected from coronary heart disease (CHD) [30].

An increased prevalence of insomnia has been reported in African Americans compared with whites, which may in part be attributable to ethnic differences in associated risk factors, such as obesity [31]. It is not known whether this is present in UK African individuals who have a much lower risk of CHD than their American counterparts [30]. It has been suggested that there may be a genetic component for this increase [32] and it would therefore be important to study both UK Africans and Africans in Africa. Diabetes and stroke are high in UK Africans as well as African Americans.
differences in inflammatory markers have been observed [28] which in part are associated with ethnic differences in cardiovascular risk. It is important that future studies investigate whether ethnic differences in CHD, diabetes and stroke are in any way related to differences in sleep disorders and whether or not there may be an underlying inflammatory component.

**Obesity, Sleep and Inflammation**

Obesity is associated with an increase in SDB and OSA (SAS) [33]. Obesity is becoming a global epidemic in both adults and children and is associated with an increased risk of morbidity and mortality as well as reduced life expectancy [34]. It is clear that obesity may have its effect on CVD through a number of different known and possibly as yet unknown mechanisms. These include dyslipidemia, hypertension, glucose intolerance, inflammation, OSA/hypoventilation, and the prothrombotic state [34]. Obesity leads to a change in an individual’s metabolic profile and an accumulation of adipose tissue.

Lack of sleep may have an effect on the development of obesity and subsequent CVD through a number of mechanisms. Spiegel et al, in the first randomized cross-over clinical trial of short-term sleep deprivation, demonstrated that sleep deprivation was associated with decreased leptin and increased ghrelin levels [35]. This in turn would lead to a co-comitant increase in hunger and appetite, increased insulin resistance and accumulation of fat and decreased carbohydrate metabolism Fig. (3). The individuals in this study were subjected to extreme acute sleep deprivation (<4 h per night) and further studies are required to determine the effects on these hormones of more modest sleep deprivation (<5 h per night), especially in the long-term [35]. A study of 422 children (boys and girls of primary school age (5-10 years)) has demonstrated an association between sleep duration and the risk to develop childhood overweight/obesity [36]. Interestingly, the Nurses Health Study demonstrated that while short sleep duration leads to an increase in weight with time there was no evidence to suggest that this was the result of an increase in appetite [37]. These findings are in contrast to others that have demonstrated a clear relationship between duration of sleep, ghrelin, leptin and appetite [35,38]. The findings from the Nurses Health Study suggest that perhaps the effects of sleep on obesity occur as a result of a change in energy metabolism. Uncoupling proteins are proteins that

**Fig. (3). Effect of the lack of sleep on energy regulating hormones**
uncouple proton exchange and ATP production. Polymorphic variation in these genes has been related to energy metabolism, obesity and diabetes [39, 40]. Furthermore, Cirelli et al demonstrated that in animal studies, sleep deprivation was associated with an increase in Uncoupling Protein 2 (UCP2) expression in liver and skeletal muscle [41]. The latter is the largest tissue in the body, and hence increased UCP2 expression in this tissue may have a potentially large effect on resting energy expenditure [41].

Inflammatory process may also underlie the effect of sleep on weight gain. Recent studies have shown the importance of adipose tissue as an endocrine organ which is capable of secreting, among others, inflammatory cytokines [42]. It is therefore possible that a lack of sleep acting via the regulatory hormones above may lead to an increased fat accumulation and increased secretion of pro-inflammatory cytokines. There is evidence to suggest that inflammatory processes may be important in obesity and may mediate some of the effects observed with increased weight. We demonstrated that an approximate 2% increase in soluble E-selectin level is associated with a 1 unit higher BMI and a 0.01 unit greater Waist-hip ratio (WHR) [43]. Adiponectin, which is a protective cytokine however, is not reduced in patients with OSA compared with matched controls without OSA [44]. In a separate study, individuals with OSA who underwent CPAP treatment had associated changes in inflammatory markers (IL-6 and ICAM-1) [45]. The levels of the inflammatory markers were also associated with resistin levels. Likewise, CPAP treatment decreased the levels of ICAM-1 and IL-8 [46]. Prospective, longitudinal studies however are required to examine the causal link between sleep and obesity and inflammatory mediators.

Glucose and Insulin Regulation, Diabetes, Sleep and Inflammation.

Diabetes can lead to the development of sleep abnormalities. Findings from the Sleep Heart Health Study indicated that diabetes is associated with periodic breathing, a respiratory abnormality associated with changes in the central control of ventilation [47]. It is thought that diabetes may bring about sleep abnormalities as a result of its deleterious effects on central control of breathing. However, it is also important to note that sleep loss is associated with a decrease in glucose tolerance, a higher evening cortisol level and increased sympathetic activity Fig. (4). Treatment for OSA has also been associated with beneficial changes in insulin sensitivity [45]. Further studies are required to investigate whether sleep loss can predict changes in glucose metabolism or vice versa.

Laboratory studies of healthy young adults, demonstrated that recurrent partial sleep restriction was associated with alterations in glucose metabolism including decreased glucose tolerance and insulin sensitivity [48]. Furthermore, sleep restriction led to changes in appetite control, in that the
levels of the anorexigenic hormone leptin were decreased, whereas the levels of the orexigenic factor ghrelin were increased (see previous Figure (effect of sleep on energy regulating hormones)). These changes were associated with an increase in hunger and appetite. Over a long period this may lead to weight gain, insulin resistance and Type 2 Diabetes [48]. A recent longitudinal analysis from the MONICA study has demonstrated that in both women and men the difficulty in maintaining sleep as opposed to the difficulty in initiating sleep was associated with a higher risk of type 2 Diabetes during the subsequent mean follow-up period of 7.5 years [10].

These and similar findings have led to the suggestion that sleep and sleep disorders may have a prominent role on metabolic and endocrine functions [49, 50]. There is a large body of evidence to suggest that oxidative stress and inflammation play a large role in the development of diabetes and the development and progression of the associated complications [51]. The exact causal pathways remain to be elucidated and likewise it remains to be seen if the diabetic complications associated with sleep disturbances have an underlying inflammatory component.

Blood Pressure, Sleep and Inflammation

Blood pressure normally displays a nocturnal dip of about 10% [52]. Non-dippers are at an increased risk of CVD and African Americans tend to display more non-dipping characteristics compared to Caucasians and this is associated with an increase in sleep disordered breathing [53]. SDB has been identified as a risk factor for adverse cardiovascular outcomes in the elderly and is also associated with an increase in post stroke mortality [54]. Likewise evidence suggests that OSA patients have an increased incidence of hypertension compared with individuals without OSA, and that OSA is a risk factor for the development of hypertension [7]. Acute deprivation of sleep in healthy subjects leads to an increase in blood pressure and SNS activation and evidence is growing, which suggests that there is a causal relationship between OSA syndrome and hypertension. [8]. A recent longitudinal study demonstrated that short sleep duration (<5 h per night) was associated with a significantly increased risk of hypertension (hazard ratio, 2.10; 95%CI, 1.58 to 2.79) in subjects between the ages of 32 and 59 years. Furthermore, adjustment for confounding factors such as obesity and diabetes only partially attenuated this relationship [11]. Studies demonstrated an association between hypertension and inflammation but potential causal pathways remain to be examined in more detail. It is however of interest to note that patients with OSA exhibit increased resting heart rate, decreased time duration between two consecutive R waves of the electrocardiogram (R-R interval) variability, and increased blood pressure variability. As well as observed changes in inflammatory mediators such as CRP, OSA is also associated with changes in fibrinogen and plasminogen activator inhibitor [7], which are important in the development of hypertension and cardiovascular disease.

Lipids, Sleep and Inflammation

OSA may lead to hypoxia and the subsequent generation of reactive oxygen species (ROS). These in turn can lead to an increase in lipid peroxidation. Indeed, increased inflammatory markers and markers of oxidative stress have been found in patients with OSA [55]. Although a recent study concluded that systemic inflammation is a characteristic of OSA patients it failed to find any difference in lipid peroxidation or antioxidant defence (as measured by superoxide dismutase (SOD)) between patients with OSA (n=25) and controls (n=17) [55].

Metabolic Syndrome, Sleep and Inflammation

Metabolic syndrome is characterised by the clustering of cardiovascular and metabolic risk factors in a given individual. These include the presence of central obesity, an adverse lipid profile (high triacylglycerols and low high density lipoprotein (HDL)-cholesterol), raised blood pressure and insulin resistance or glucose intolerance. It has also been suggested that there may be an increased pro-inflammatory state [56]. Furthermore, Vgontzas et al. [57] clearly demonstrated that inflammatory cytokines are increased in individuals with OSA and they proposed that these cytokines were the mediators of excessive daytime sleepiness (EDS). They demonstrated the importance of visceral fat in OSA syndrome. They suggested that sleep apnea and sleepiness in obese patients may be manifestations of the metabolic syndrome. Indeed in the US, data from the Third National Health and Nutrition Examination Survey (1988-1994) has shown that in the US population the prevalence of the metabolic syndrome parallels the prevalence of symptomatic sleep apnoea in general random samples [57].

Inflammation and Sleep

Immune molecules alter sleep architecture and sleep deprivation alters neuroendocrine and immune response [58]. Furthermore, immune system activation and neuroendocrine responses alter sleep [58]. In addition, sleep quality may affect susceptibility to infection, as well as ones ability to fight off infection [59]. The concentration of high-sensitivity CRP (hsCRP) is predictive of future cardiovascular morbidity [60] and at the same time short sleep duration and sleep complaints are associated with increased cardiovascular morbidity [9,23]. CRP levels are elevated following both acute total and short term partial sleep deprivation [23]. Compared with control subjects the levels of TNF-α, IL-6, hsCRP, adhesion molecules, and monocyte chemoattractant protein-1 are markedly and significantly elevated in patients with sleep apnoea [61]. Short term sleep deprivation gives rise to a number of effects on the immune system including a decrease in cellular immune response on the following day [2, 62]. Likewise, the immune response to viral challenge is also reduced [63]. It remains to be elucidated whether similar effects on the immune system are observed in individuals with long-term sleep deprivation.

As well as infectious agents, it is known that other diseases can lead to an increase in systemic inflammation such as arthritis. Studies in patients with rheumatoid arthritis have revealed patterns of sleep disturbances that are not associated with the concomitant pain [64]. The innate immune system pathway can be activated by the outer lipopolysaccharide (LPS) component of bacterial cell membranes [65]. Such stimulation of the innate immune system occurs through toll-
like receptors and can lead to an increase in inflammatory cytokines Fig. (5).

LPS increases NREM and reduce REM sleep in rabbits [66]. In rats, a 30 day infusion of LPS led to a loss of hypocretin neurons. This suggests that LPS and the resulting inflammation may play a role in the loss of hypocretin neurons which occur in sleep disorders such as narcolepsy [67].

In human studies, Gundersen et al. [68] investigated the effect of prolonged physical activity with concomitant energy and sleep deprivation on leukocyte function. They demonstrated that leukocytes responded with an increasing release of inflammatory cytokines when challenged with LPS as the study progressed. Furthermore, they found that the response to the anti-inflammatory agent hydrocortisone was reduced. These results demonstrate that multifactorial stress can activate immune cells and prime their response to a microbial challenge [68]. However, it is important to note that sleep deprivation can alter catecholamines [69], which in turn may have an effect on white blood cells. The exact part played and the importance of the sleep deprivation in this multifactorial stress needs to be further investigated.

The intermittent hypoxia/reoxygenation process that occurs in OSA syndrome is associated with a selective activation of inflammatory processes as demonstrated by the increase in circulating tumour necrosis factor-alpha (TNF-alpha) and NFkappaB levels whereas adaptive pathways as determined by the measurement of the adaptive regulator HIF-1 are not increased [70]. Furthermore, CPAP therapy is able to normalise the increased TNF-alpha levels [70]. OSA syndrome is associated with an increased monocyte NF-kappaB activity. Moreover this is also associated with an increased expression of INOS protein [71]. Further information on the links between the innate immune system and sleep can be found in a recent review [3].

Cortisol, Sleep, the Sympathetic Nervous System (SNS), Hypothalamic Pituitary Adrenocortical (HPA)-Axis and Inflammation

Dysfunction of the HPA axis at any level (corticotrophin releasing hormone (CRH) receptor, glucocorticoid receptor, or mineralocorticoid receptor) can disrupt sleep [72]. Sleep, and in particular deep sleep, has an inhibitory influence on the HPA axis, whereas activation of the HPA axis leads to arousal [72]. Furthermore, excessive daytime sleepiness, such as present in sleep apnoea, narcolepsy, and idiopathic hypersomnia are associated with an increase in the secretion

![Diagram](image_url)

Fig. (5). Possible interaction between the innate immune system and sleep regulation
of inflammatory markers [73]. It has also been suggested that HPA axis hyperactivity may be a consequence of OSA and may indeed contribute to secondary pathologies such as hypertension and insulin resistance. [72]. On awakening, there is a rise in cortisol levels. The time of awakening and stress are thought to influence the magnitude of the cortisol awakening response (CAR) [74]. A recent study which examined men and women London Underground shift-workers suggested that early-waking, stress early in the day, and associated cortisol levels often coincide with sleep disturbance. [74]. In a recent pilot study, which examined the sleep and the stress-induced cortisol response in children and adolescents, there were significant associations between the self-reported sleep quality but not quantity and the cortisol response [75].

**Depression, Sleep and Inflammation**

When compared with controls depressed patients have a significant nocturnal increase in circulating IL-6 and sICAM [76]. Furthermore both sleep latency and REM density are associated with these inflammatory markers [76]. It is of interest to note that in patients with depression, total sleep deprivation leads to an increase in renin secretion and a concomitant trend for a decrease in HPA axis activity in the recovery night [77]. It has been suggested that these changes could be a "fingerprint" of a rapidly antidepressive treatment [77].

**Social Economic Status (SES), Sleep and Inflammation**

Low SES is frequently associated with sleep deprivation and ethnic differences in SES and sleep patterns exist [78]. African American children have an increase in sleep disordered breathing compared with white Caucasians which could contribute to an increase in inflammatory processes and associated CVD risk [79]. However, further studies are required to examine this hypothesis.

**Alcohol, Sleep and Inflammation**

There is some inconsistency in the literature but in general it is accepted that moderate-to-large quantities of alcohol are capable of aggravating severe OSA [80]. It has also been suggested that there are inter-relationships between alcoholism, sleep loss and ethnicity, which may also operate in a bidirectional manner [81]. It has been postulated that disturbed sleep patterns effect hormonal, autonomic nervous system and immune function and might contribute to the increased mortality rate observed in American African alcoholics [81].

**Paediatrics, Sleep and Inflammation**

Children with sleep disordered breathing have higher CRP levels than children who do not [82]. Furthermore, 94% of the children studied who had elevated CRP levels also reported excessive daytime sleepiness or learning difficulties as compared to 62% of children who had CRP levels in the normal range [82].

**Genes, Sleep and Inflammation**

In the brain the sleep-wake cycle is regulated by the central circadian oscillator in the hypothalamic suprachiasmatic nuclei (SCN) [83]. This oscillator is composed of many genes and proteins which interact together and have both positive and negative feedback loops [83]. Among others, the CLOCK and BMAL1 elements promote the expression of the Period (peri, 2 and 3) and Cryptochrome (Cry1 & 2) genes. It is known that genetic variation in some of these genes, including Period 2, is important in the development of some sleep disorders [84].

If it is possible to identify genes and gene products which contribute to sleep disorders it would be interesting to study their associations in children, as well as adults, as the former are less likely to be influenced by age-associated comorbidities, which are present in the adult populations. However, sleep disorders do exist in some children which need to be excluded or diagnosed in such studies.

A recent literature review led to the suggestion that inflammatory cytokines such as TNF-alpha and Interleukin-1(II-1) perform neural functions in normal brains As such they should be regarded as both neuromodulators as well as inflammatory mediators [85]. The genes coding for these cytokines and their accessory proteins are expressed by glial cells and neurons in the normal brain [85]. Receptors for these cytokines are present on neural cells [85]. Patients with OSA syndrome have elevated TNF-alpha levels [86]. The -308A TNF-alpha gene polymorphism is responsible for increased TNF-alpha production. Individuals with OSA syndrome and their siblings are more likely to carry this polymorphism than population controls; once more indicating that an increase in inflammatory mediators may be important in the pathogenesis of OSA syndrome [87].

Genetic and environmental factors may act together to influence the set-point at which a given individual's neuroendocrine stress responses and cytokine production patterns respond to different pathogens or antigens [88]. It is therefore possible that genetic determinants of sleep acting on the oxidative and immune pathways may also be of importance in determining an individual's subsequent cardiovascular risk.

**Sleep and Pharmacological Treatments**

OSA is characterized by a collapse of the airway that occurs during sleep [89]. As a result there is a lack of oxygen to the brain and the individual wakes up so that breathing is resumed [89]. This can be repeated several times in one night and results in fragmented sleep. One of the most common treatments for this condition is CPAP [89]. This maintains the airway during sleep. However, in some individuals the daytime sleepiness associated with OSA and other sleep disorders is not always eliminated by this treatment. Although the exact mechanisms that govern the sleep-wake cycle and the process are unknown. It is of interest to note that a relatively new drug, Modafinil is effective against excessive daytime sleepiness [90]. It would appear that this drug exerts some of its action in the hypothalamus, which is an area of the brain that regulates sleep-wake functioning [90].

5-hydroxytryptophan (5-HT) increases serotonin levels and is used to treat depression [91]. There has been some suggestion that it may improve sleep patterns and aid weight loss. A recent study, which investigated the effect of sleep deprivation on 5-HT turnover, indicated that REM sleep
modulated the 5-HT turnover in the brain in a region-specific manner [92].

Given the suggestion that poor sleep may have cardiovascular consequences as a result of its effect on the inflammatory and oxidative pathway, it is possible that the pharmacological management of sleep disorders may need to include anti-inflammatory and antioxidant agents as well.

The Importance of Sleep

Sleep is a fundamental requirement for living individuals. In this review we discussed how changes in sleep, acting through inflammatory mechanisms, may be associated with an increased risk of CVD. Changes in working patterns and increased demands on individual's time require that more individuals are awake for longer periods of time. Unfortunately, increases in shift work, on-call rota's and prolonged working hours result not only in a potentially increased cardiovascular risk but also an increased risk of fatigue and accidents e.g. road traffic accidents, commuter train disasters and pilot error as well as medical errors [93,94]. Driving while drowsy has a similar effect to driving under the influence of alcohol. It is believed that substantial numbers of medical errors result from fatigue due to adverse sleep patterns in nurses and doctors [4]. These problems have a high cost both in terms of human life and economic factors. Hence, it can be seen that sleep has a major impact on our health and well-being and needs to be researched thoroughly. Some of these problems associated with the lack of sleep could be addressed by improving our understanding of the biological basis of sleep; the biochemical mechanisms; involved, by increasing awareness both among health professionals and among the lay public, and by making changes to work patterns and access to sleep recovery (naps/ time off) as well as improved diagnosis and treatment regimes.

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