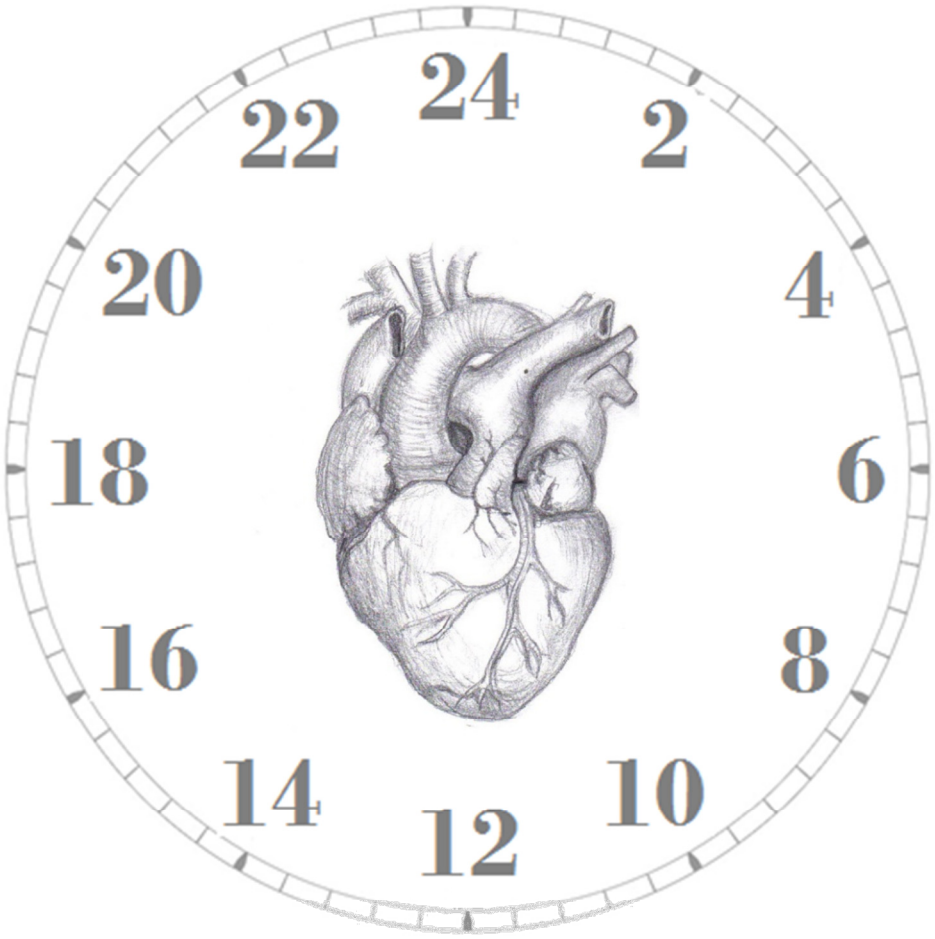
BACHELOR THESIS

WHY DOES SHIFT WORK INCREASE THE RISK OF CARDIOVASCULAR HEART DISEASE?



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Summary

Humans are diurnal, which means that most of their activity occurs during the light phase of the day. The rhythmic alternation of activity and rest is regulated by a circadian clock in the hypothalamus. Due to this rhythm, the whole body is under 24-hour regulation. This includes among others the immune system and various metabolisms. Living out of synchrony with the biological clock can cause health problems, like cardiovascular disease (CVD). Shift work, for example, can cause such a desynchronization. Due to the development towards a 24-hour society, there are increasing numbers of people working in shifts, and therefore have an increased risk of CVD. Knowing this, the question 'why does shift work increase the risk of CVD?' arises and this will be the leading question of this thesis. Three stress-pathways have been indicated that can increase this risk due to shift work, namely the behavioral, psychological, and physiological stress-pathways. Via these pathways, many homeostatic processes can be disturbed, which can eventually lead to CVD. This includes high cholesterol levels, increased blood pressure, increased heart rate, and an increased risk of diabetes and metabolic syndrome (MetS). Though many studies have shown the increased risks via these pathways, the different designs of the studies could be influencing the resulting interpretations. Therefore there is still a lot to be done to give a final conclusion about this subject.

Introduction

Humans have a 24-hour rhythm with most of their activity in the light phase of the day. All the daily activities are based on this rhythm, like work schedules, school programs, and social events. They also eat mostly at daylight, so the digestion system is activated during the day. To give an optimal balance between the energy demand and supply for the day-activities, the metabolism of the body is most active during the light phase. In addition, to give an optimal protection to infections, the immune system is activated at this phase of the day as well. The 24h rhythm in the human body requires proper temporal orchestration. Like in almost all mammals, this orchestration is accomplished by a biological clock; the suprachiasmatic nucleus (SCN) in our brain. This clock is keyed to daylight and regulates the daily rhythms of our body. The SCN does this via daily variation of gene expression, hormone secretion, and electrical activity of its cells. One of the hormones which are involved in this rhythm is melatonin, which is known as the hormone of the night. At the end of the day the concentration of melatonin rises and thereby indicates the dark phase of the day. For humans this means the rest phase, whereby almost all systems go in rest. At the end of the night, the concentration of melatonin decreases and when it is low the systems are activated: the body wakes up and is ready for the day (Buijs et al, 2003). Disruption of this circadian rhythm can cause disturbance in homeostasis and could therefore lead to health problems (Durgan et al, 2011).

Almost all mammalian cells contain a small circadian clock which, via regulation of the SCN, induces the 24-hour rhythm. This leads to a circadian rhythm of homeostasis of the human body. The cells which are involved in the functioning of the heart, like cardiomyocytes, vascular smooth muscle cells, endothelial cells, and fibroblast, are also influenced by the SCN. Therefore a disturbed 24-hour rhythm can lead to deregulation of cardiovascular homeostasis and in its turn could increase the risk of heart disease (Balsalobre et al, 1998; Durgan et al, 2005).

A known way of living which can disturb circadian rhythms of humans is performing shift work. These irregular work schemes force humans to work outside the 9 to 5 interval which is mostly out of synchrony with the biological rhythm. In the Netherlands, for example, more than 50% of the labor force works in irregular work schedules and more than 500 thousand people work in shifts (Becker, 2002). (Figure 1)

Figure 1: Percentage of the labor force working irregular times in the Netherlands. The percentages are further divided over the different shifts outside the 9-5 workdays (CBS, 2002).

The Third European Survey of Working Conditions conducted in 2000 showed that 22% of the people in Europe were involved in shift work (BLS, 2002). This shows that there is a huge group of people who have an increased risk of health problems due to their work. We are moving towards a 24-hour society, resulting in an increasing number of shift workers and therefore the problem of increased risk of health problem becomes bigger and bigger (Becker, 2002; BLS, 2007). Several studies, like the one of Knutsson et al in 1986, showed that there is an association with shift work and an increased risk of health problems, including heart disease (Knutsson et al, 1986). These studies have shown that the relative risk for heart disease caused by shift work is between 1 and 2, with an average of 1.4. In addition, the risk increased when the exposure to shift work increased. Knutsson et al obtained this ratio in 1986 and reviewed it in 1993 where the results were confirmed. Multiple studies replicated this research and came with similar results which are shown in figure 2. Most of the studies found a risk estimated around the 1.4. However, 4 large studies failed to find an association. The differences can be caused by the different designs of the studies and should be looked at more closely to give a definitive conclusion of the relation (Knutsson et al, 1986; Bøggild and Knutsson, 1999; Steenland et al, 1996).

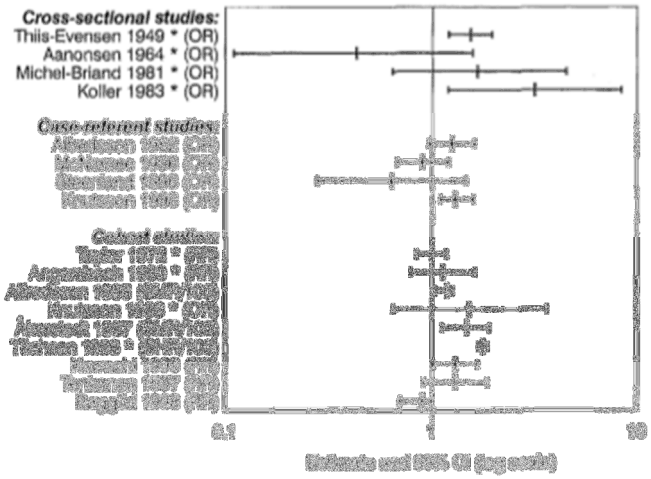

Figure 2: Relative risk of heart disease due to shift work shown by 17 studies (Bøggild and Knutsson, 1999).

Since a relation has been found in previous research, the question 'which mechanisms cause these health problems?' arises. Therefore this thesis will provide an overview of the mechanisms that cause these health problems, with a focus on cardiovascular problems and heart disease, due to shift work led by the question: Why does shift work lead to an increased risk of heart disease? To do so, a description of shift work and heart disease will be given, followed by the cause and effect of these two subjects. After that, it will close with a discussion and an implication for further research.

Shift workers

The definition of shift work given by Knauth in 2011 is ‘work at varying hours of the day or work at constant but unusual hours of the day’ (Knauth, 2011). This includes all hours which are outside the 9 to 5 work day, which is here defined as the normal working hours. It means ‘the working hours outside the normal 9 to 5 interval’, and therefore shift work is also indicated as ‘irregular working times’. In addition, a normal work week is defined as a 5 days-work schedule with 2 days off in the weekends. Therefore, working in the weekends is also seen as shift work.
Due to a move towards a 24-society more and more people have to work outside their 9 to 5 interval. More companies have to work in the evenings or even around the clock to cope with the increasing demands of 24/7 service. This involves banks, hospitals, transport, pubs, and many more. This demand forces employees to work in the early morning, the late evening or at night. To manage these working hours, people work in shifts so the 8-hour workdays remain. However, sometimes the workdays of shift workers are longer, followed by an extra rest day.
An increase in shift workers is seen in many countries. A survey over 15 European countries showed that in 2000 22% of the workforce was involved in shift work. The numbers of people working in rotating shifts was increased by 1.7% since 1995 to 16.8% (BLS, 2002). In the Netherlands the number of people working in irregular work schedules increased since 1992 with 7% to 55% in 2002 (Becker, 2002). In 2008 the numbers were further increased to 60% (Beckers and Kösters, 2009). This increasing trend is also seen in the United States of America, where the number of Americans working in irregular work schedules is increased from 13.4% in 1985 to 29.7% in 2004 (BLS, 2007). (Figure 3)

	1985	*1991*	*1997*	*2001*	*2004*
Total, 16 years and older	13.6	16.0	29.9	30.7	29.6
Men	13.9	15.9	30.0	30.8	29.3
With own children under 18 years	13.1	15.6	30.7	31.8	29.8
Women	13.2	16.0	29.7	30.6	29.9
With own children under 18 years	13.3	16.3	30.8	30.7	30.2

Figure 3: percentage people working in irregular working schedules in the United States of America, shown from 1985 to 2004 (BLS, 2007).

The irregular working times of shift workers induce a circadian mismatch, which means their activity pattern diverges from their natural pattern influenced by the SCN in the brain. This mismatch resembles a jet-lag in the human body, where many rhythms which are under the control of the SCN are disrupted or deregulated. To adapt to the newly imposed rhythm of activity and rest, the SCN has to adjust. With shift work, the SCN cannot adjust fast enough and therefore the body stays deregulated and can result in different types of health problems, like heart disease. The effects of shift work on the SCN are not identical to everyone. There are various factors which can influence the sensitivity of a person to these jet-lags; like age, gender, type of work, and social class (Knutsson et al, 1986). This probably implies that the risks for heart disease and other health problems are not similar for everyone. Therefore, individual differences should be taken into account, which makes the research with shift workers a little more complicated.
Now that the definition of shift work for this study is established, a closer look at the definition of heart disease is taken in the next section.’

Heart Disease

Cardiovascular disease (CVD), or heart disease, is a class of diseases that involves the heart, the blood vessels (arteries, capillaries, and veins), or both (Maton, 1993). This includes cardiac disease, vascular diseases of the brain and kidneys, and peripheral arterial disease (IOM, 2010). There are various factors that can increase the risk of heart disease in humans, with atherosclerosis as the main pathological process. Atherosclerosis is a process where the artery walls thicken as a result of invasion and accumulation of white blood cells. It causes an endothelial dysfunction and a blockade in the blood vessels. An endothelial dysfunction is defined as an imbalance between vasodilation and vasoconstriction, which decreases the functionality of the veins. This process in turn is caused, among other things, by elevated blood pressure, abnormal blood lipids, elevated blood glucose, plasma homocysteine, and C- reactive proteins. C-reactive proteins are predictors of the risk of stroke and myocardial infarction and therefore a risk factor of heart disease. Due to the many risk factors of atherosclerosis, there are also many factors that can increase the risk of CVD via this process, like obesity, physical inactivity, and smoking (WHO, 2007). Thereby, atherosclerosis is not the only process which increases the risk of CVD. Also the metabolic syndrome (MetS) and diabetes can increase this risk (Antoniades et al, 2009; Peters et al, 2014). MetS is a clustering of cardiac health risk factors, such as insulin resistance, hypertension, cholesterol abnormalities, and central obesity (Galassi et al, 2006). Diabetes, type 2 in particular, leads to many conditions which can increase the risk of heart disease. This includes high blood pressure, abnormal cholesterol levels, and high triglycerides levels (AHA, 2012). Due to the many factors that can increase the risk of heart disease, it's a very common disease over the whole world and therefore an important subject for many studies including the studies of shift work. Due to a disruption of the circadian rhythm by shift work, many systems in the body can deregulate and in their turn increase the risk of heart disease. The different pathways which can lead to an increased risk of CVD caused by shift work are given below.

Cause and effect

To substantiate the relation between shift work and heart disease, Knutsson and Bøggild have shown that there are different, though interrelated, stress-pathways which may lead from shift work to health problems in general (Knutsson and Bøggild, 1999). This model in figure 4, which is adapted by Puttonen et al (2010) to also include CVD, is also useful in the study at hand. Therefore the model will be discussed below. (Figure 4)

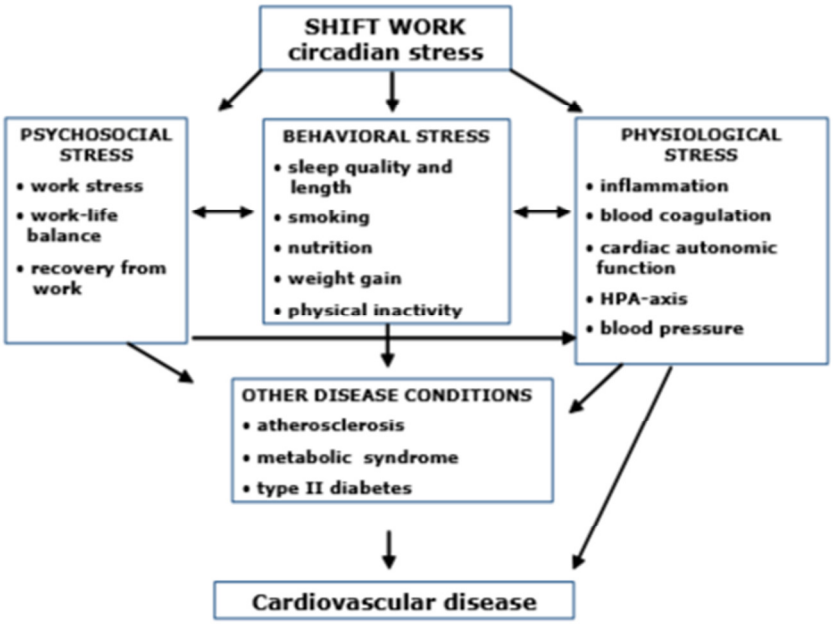

Figure 4: A model proposed by Knutsson and Bøggild and elaborated to a model for cardiovascular disease by Puttonen et al which shows the pathways that may lead from shift work to cardiovascular disease (Puttonen et al, 2010).

Behavioral stress

Shift work leads to a circadian mismatch which has immediate influence on the length and quality of sleep. This is mostly seen with people who work night shifts. However, it is also seen in the early-morning shift and the late-night shifts. These working times force a worker to sleep when there is a lot of light from the sun and when the remainder of the society is awake. This makes it very difficult to fall asleep or to stay asleep, with insomnia, sleep debt, and/or excessive daytime sleepiness as result (Åkerstedt et al, 2008). Insufficient sleep can lead to many health risks. The sympathetic nervous system gets activated for example, causing blood pressure and heart rate to increase, the evening cortisol to rise, and the glucose tolerance to decrease (Mullington et al, 2008). Furthermore, insufficient sleep leads to a decrease of leptin levels and therefore increases feelings of hunger with increased food intake as a result (Spiegel et al, 1999). In addition to the activation of the sympathetic nervous system, sleep deprivation increases peripheral circulation of leukocytes, interleukins, and C-reactive protein. The increase of leukocytes and interleukins increase the inflammation in the body, which is an important factor for the process of atherosclerosis (Van Leeuwen et al, 2009). The effect of shift work on sleep length depends on whether the shifts are permanent or rotating, where rotating shifts have a greater impact.

In addition to sleep loss, the behavior of shift workers also changes. One of these changes is the incidence of smoking behavior. Studies reported an increase in smoking behavior in shift workers compared to day workers (Knutsson et al, 1986; Bøggild et al, 1998). However, a study of Knutsson and Nilsson has shown that the social class of workers influences the amount of shift work done, as well as the amount of smoking. Therefore the status of the workers (instead of shift work) might explain the increased smoking behavior which is seen in several studies (Knutsson and Nilsson, 1998). This indicates that there is still a debate about whether shift work increases smoking behavior, and

therefore increased smoking cannot yet be taken as a factor to explain the increased risk of heart disease. Apart from smoking, dietary intake also was indicated to be increased due to shift work. Both the amount of food intake and the timing were different compared to day workers, where the energy consumption was the highest in night workers. These differences in food intake could lead to a metabolic disturbance and therefore cause health problems (Morikawa et al, 2008).
Finally, a decrease of physical exercise and an increase in alcohol consumption were reported to be related to shift work. However, several studies found no effect of shift work on these two aspects. Hence not every shift worker experiences decreased physical activity or increased alcohol consumption, and therefore these aspects not always cause an increased risk of CVD.

Psychological stress

Working at irregular times also has an effect on psychological factors that can increase stress levels. One factor that is shown to be a stressor is the lack of feeling in control of your working times. When humans lose the perception of feeling in control, they automatically are more stressed compared to the times they perceive to have hold on their working times (Parkes et al, 1999). Another factor that increases the psychological stress due to shift work is the imbalance between work and social life. The irregular working schedules of people performing shift work, mostly including the nights, interfere with social activities and reduce the time for family, physical activity, and recreation. This mismatch with the family-pattern can lead to a lack of social support of shift workers, and therefore disturbs the work-life balance (Pisarski et al, 1998). Furthermore, a factor that has a great impact on work stress is the perceived recovery from work. Shift workers report to have less recovery time, or not the recovery time needed after a shift. The perceived amount of recovery needed is higher after shift work compared to day work. This combined with shorter sleep duration and disturbed life-work balance which decreases the amount of recovery, leads to insufficient recovery and therefore more stress and illnesses (Van Amelsvoort et al, 2004). However, certain aspects influence the amount of stress or the perceived amount of stress caused by these stressors. One of them is the socioeconomic status of a person, where the stress is perceived higher with unskilled workers and lower civil servants (USC, OTA, 1991). Other factors are personal characteristics, age, and gender which were mentioned in the section above, when defining shift work for this study.

Physiological stress

A circadian mismatch caused by shift work has a major impact on the physiological processes in the body. When a human is active during the time when he should be in rest, the sympathetic instead of the parasympathetic nervous system is activated. This is shown in for example enhanced evening cortisol levels (Chung et al, 2007). This activation leads to various processes which can disturb homeostasis of the body and therefore increase the risk of CVD. For example, higher sympathetic activity enhances blood pressure and heart rate (Baumgart et al, 1989). As is shown before, these factors increases the risk of atherosclerosis, and therefore of CVD. Other factors which are activated by the sympathetic nervous system and increase in their turn the risk of atherosclerosis are inflammatory factors. The nervous system activates the immune system and therefore the peripheral circulation of leukocytes, interleukins, and C-reactive proteins increases (Sookoian et al, 2007). This results in an inflammatory response in, among other things, the blood vessels, leading to an accumulation of white blood cells in the veins. The inflammation also leads to an endothelial dysfunction, which decreases the balance between vasoconstriction and vasodilation. These two processes combined cause the blood vessels to narrow, which is known as atherosclerosis. Finally, decreased NK-cell activity is seen during the night shifts, which indicates that the night shift itself induces high physiological stress levels (Kobayashi et al, 1997). This makes the immune system vulnerable in response to these shifts and therefore increases the risk of infections and other health problems.
A study of Martins et al showed that shift work also increases the plasma homocysteine levels in the body (Martins et al, 2003). These levels are an independent risk factor for atherosclerosis and CVD

and influences several risk mechanisms of CVD, like an increase of endothelial dysfunction, oxidative stress, and atherogenic inflammation. Atherogenic inflammation has a vasoconstrictor effect and therefore increases blood pressure and also decreases endothelial function.
Next to atherosclerosis, there are other pathological processes which can increase the risk of CVD. Studies have shown that shift work is associated with risk factors for metabolic syndrome (MetS), which is one of these processes (Biggi et al, 2008; Ghiasvand et al, 2006). MetS is a clustering of cardiac health risk factors, and therefore shift work can lead to MetS via various pathways. One of these pathways is hypertension. This is a chronic high blood pressure and therefore increases the risk of CVD. This high blood pressure, as is shown before, is among others caused by an activation of the sympathetic nervous system, endothelial dysfunction, and atherogenic inflammation.
Working in night shifts forces one to eat at other times of the day compared to normal day time work. This leads to an increased food intake at night. This happens while the body is not (yet) adapted to these eating patterns during shift work, and therefore not ready to digest the food properly. This can lead to unbalance of homeostasis and can therefore enhance cholesterol levels in the body (Lelmernas et al, 1994). High cholesterol levels can increase the risk of atherosclerosis and other health issues and is therefore a huge risk factor for CVD. In addition, the cholesterol levels are also increased by reduced physical activity, which can also be a result of shift work (Marqueze et al, 2013).
Next to atherosclerosis and MetS, diabetes is another pathological process which leads to CVD. Studies have shown an increased incidence of type 2 diabetes among shift workers (Depner et al, 2014). Diabetes increases the risk of heart disease via many ways, and can also be the origin of other homeostatic dysfunctions, like increased cholesterol levels.
One important homeostatic process to support the functioning of the body, which is also circadianly regulated, is oxygen supply. A mismatch between supply and demand of oxygen to the myocardial cells can cause myocardial infarction or angina pectoris. However, this issue is not proven in studies yet and therefore still requires further research.

Discussion

This study set out to find an answer to the question: 'Why does shift work lead to an increased risk of heart disease?'. Many studies have shown a wide variety of mechanisms which can increase the risk of heart disease by shift work. The three pathways indicated by Knutsson and Bøggild, namely physiological, behavioral, and psychological stress-pathways, were used in many studies to address this issue systematically. Yet, there are factors that influence the outcome and should be taken into account when looking at the results and conclusions of the various investigations. It has been demonstrated that age, gender, type of work, and social class influence the amount of risk to a shift worker. However, these confounding factors are not always kept constant in all studies, which can affect the conclusions reached in the articles. For example, Chung et al did research with female nurses to look at the enhanced sympathetic nervous system during permanent night shifts (Chung et al, 2009). Steenland et al did research with male subjects to look at the effects of shift work on the risk of heart disease (Steenland et al, 1996). Sookoian et al and Knutsson et al investigated male subjects in their study of the impact of shift work on heart disease (Sookoian et al, 2007; Knutsson et al, 1986). It should be taking into account that the results of the various studies could be different in the other sex. Another factor of influence is job function, which also differs between the studies. Looking at the different investigations, Sookoian et al used factory workers to prove increased metabolic syndrome (MetS) incidence and inflammation, while Marqueze et al used truck drivers to show the increased risk on CVD by irregular shifts (Sookoian et al, 2007; Marqueze et al, 2013). These jobs are different in many ways, and therefore they may generate different effects. Working in the factory can increase the incidence of inflammation, where driving a truck can have no effect on these parameters and vice versa. Though it is hard to test this with all the jobs in the world, the conclusion should be taken with care. The last factor discussed here is the influence of age. Different age groups were used, where shift work has a larger effect in the groups of older shift workers. For example, Martins et al used male bus drivers between 31 and 51, and Knutsson et al used all male shift workers older than 20 (Martins et al, 2003; Knutsson et al, 1986). Here, the group of Knutsson et al is more spread and also includes the workers of 50+ where Martins et al excludes these workers. Knowing this group has a larger risk due to their higher age, the results could differ.

In addition to these three factors of influence, one other important aspect should be mentioned before conclusions can be drawn. The definition of shift work which is used now is given by Knauth in 2011 (Knauth, 2011). However, most of the studies included in this thesis, which are used as reference for further research, were done before 2011. The much referred research of Knutsson et al used subjects with a three-shift rotation schedule, which are morning, afternoon, and night shifts, rotational with rest day (Knutsson et al, 1987). Åkerstedt et al used workers with irregular working hours, including night shifts (Åkerstedt et al, 2008) and Steenland et al compared the three-shift rotation schedule to estimate increased risk of heart disease (Steenland et al, 1996). Chung et al used nurses working in the night shifts and Marqueze et al used, just like Martins et al, all people who worked with irregular shifts (Chung et al, 2009; Marqueze et al, 2013; Martins et al, 2003). These different applications of the definition 'shift workers' can influence the data found and in their turn the conclusions of the studies. This could be the explanation of the differences between studies. For example the statement about the main subject: a significant, or non-significant, relation between shift work and CVD. In addition, this could also explain the different conclusions about smoking behavior, alcohol usage, and physical activity in shift workers.

Knowing that these differences between the studies occur, researchers should bear this in mind for further studies to control for these differences to see if these variations can influence the results given by the previous studies. Nevertheless, the relation between shift work and CVD is shown to be there, which makes the studies about this subject necessary to give an insight into all the mechanisms behind it and to give a guideline for the prevention and therapy of CVD caused by shift work.

Implication for further research

Due to a lack of consistency between the studies, a large study has to be done to cover for all the factors of influence. An example of such is a study which creates a database of all the people in the workforce. This database can be obtained by asking all of the people involved to fill in a biannual questionnaire. In this form the following information can be asked: age, sex, job function, working times (usually), performance of shift work, work-life balance, smoking behavior, physical activity, alcohol consumption, amount of sleep, perception of recovery after work, dietary intake (including the times of the day), and health status. Most of these questions can be answered with either 'yes or a no' and others can be answered by defining a number on a scale from '1 to 10' which makes it fast and easy to answer. The form will be available on the internet and on a special phone application. Therefore it will be accessible for almost everyone. An e-mail will be sent twice a year as a reminder of the questionnaire to obtain as much information as possible. People with the phone application will get this reminder via a pop-up on the mobile phone. The questionnaire will be voluntarily and the information obtained will be strictly anonymous. The study can be done for many years to give a good time line and to gather a lot of information.

The information obtained from this questionnaire can give an overview of the workforce and the number of people working in shifts. In addition, a good image of the health problems in relation to shift work can be given, while the different factors of influence can be taken into account. Moreover, these factors can be compared with each other to determine the amount of influence. This information can be very useful for further research about this subject and can contribute to a better understanding of the problems around shift work.

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