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Shift work and cardiovascular disease

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SHIFT WORK AND CARDIOVASCULAR DISEASE

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ABSTRACT

Shift work is a work schedule being the opposite of normal daytime work, often defined as working time outside normal daytime hours (06:00 to 18:00). In recent years, shift work has been associated with an increased risk of numerous chronic conditions including for example cardiovascular disease, some types of cancer, type II diabetes, and the metabolic syndrome. While some studies on the association between shift work and chronic disease have found results supporting it, others have not. Therefore, more research is needed to clarify potential associations.

The aim of this thesis was to further study the proposed association between shift work and cardiovascular disease. This was addressed by performing two studies, one analysing if shift workers had an increased risk of ischemic stroke compared to day workers. The other study analysed whether shift workers had an increased risk of short-term mortality (case fatality) after a myocardial infarction compared to day workers. The studies were performed using logistic regression analysis in two different case-control databases

The findings from the first study indicated that shift workers did not have an increased risk of ischemic stroke. The findings from the second study showed that male shift workers had an increased risk of death within 28 days after a myocardial infarction; the results did not indicate an increased risk for female shift workers. The results from both studies were adjusted for both behavioural and medical risk factors without affecting the results. The findings from this thesis provide new evidence showing that male shift workers have an increased risk of death 28 days after a myocardial infarction, however more research is needed to clarify and characterise any such potential associations.

Keywords: Shift work, epidemiology, cardiovascular disease, stroke, case fatality

SAMMANDRAG

Skiftarbete definieras ofta som arbetstid som bedrivs utanför tiden för normalt dagarbete (06:00 till 18:00). På senare tid har skiftarbete associerats med en ökad risk för ett antal kroniska sjukdomar så som kardiovaskulära sjukdomar, vissa typer av cancer, diabetes typ 2 och det metabola syndromet. Dock har dessa associationer ifrågasatts eftersom ett antal studier inte har lyckats verifiera associationen ifråga, därav behövs mer forskning för att verifiera eller förkasta associationen mellan skiftarbete och kronisk sjukdom.

Syftet med denna uppsats var att ytterligare studera associationen mellan skiftarbete och kardiovaskulär sjukdom. Detta gjordes genom att genomföra två studier, den första syftade till att analysera om skiftarbetare hade en högre risk för ischemisk stroke. Den andra studien syftade till att analysera om skiftarbetare har en förhöjd risk att dö kort tid efter en hjärtinfarkt. Studierna genomfördes i två olika fall-kontrolldatabaser och resultaten analyserades med hjälp av logistiska regressionsmodeller.

Resultatet från den första studien visade ingen förhöjd risk för skiftarbetare att drabbas av ischemisk stroke. Resultaten från den andra studien visade att män som arbetar skift har en förhöjd risk att dö inom 28 dagar efter en hjärtinfarkt. Ingen sådan riskökning återfanns för kvinnliga skiftarbetare. Resultaten från båda studierna förblev konstanta trots justering för både sociala och medicinska riskfaktorer.

Resultaten av denna uppsats ger nya bevis genom att visa att manliga skiftarbetare har större risk att dö inom 28 dagar efter en hjärtinfarkt. Dock behövs mer forskning på området för att bekräfta eller förkasta dessa fynd.

LIST OF PAPERS

This thesis is mainly based on the following two papers, herein referred to by their Roman numerals:

Paper I Ischemic stroke and shift work.
Hermansson, J., Gillander Gådin, K., Karlsson, B., Lindahl, B., Stegmayr, B., & Knutsson, A.
Scandinavian Journal of Work Environment & Health (2007), 33(6), 435-439.

Paper II Case fatality of myocardial infarction among shift workers.
Hermansson, J., Gillander Gådin, K., Karlsson, B., Reuterwall C., Hallqvist J,. & Knutsson, A.
In manuscript

TABLE OF CONTENT

1. INTRODUCTION

A number of studies have shown that shift work is associated with coronary heart disease (CHD), but the evidence on a causal relationship is limited. CHD and ischemic stroke have many common risk factors, such as hypertension, smoking, and type II diabetes, but only a few studies have investigated the potential association between shift work and ischemic stroke, and the results were not conclusive. Because shift work is increasing in prevalence and cardiovascular disease (CVD) is an established public health issue, this is a field in need of further focus. In this thesis, the aim was to explore the connection between shift work and CVD further with a focus on ischemic stroke, and to study case fatality among shift workers with incident cases of myocardial infarction (MI).

1.1. Shift work

Shift work is a term used to define a work schedule being the opposite of normal daytime work, involving non-standard, non-regularly occurring working hours, and night work. This results in different type of work schedules being characterised as shift work.

It has been estimated that about 20% of the European working population are to some extent involved in shift work (working time outside normal daytime hours (06:00 to 18:00) (European foundation for the improvement of living and working conditions, 2007). As a way of organising working schedules, shift work is more prevalent in industrial production, hotels, restaurants, transport, and healthcare (European foundation for the improvement of living and working conditions, 2007; European foundation for the improvement of living and working conditions, 2010).

1.2. Cardiovascular disease

CVD is a group of diseases that involves the heart, vascular diseases of the brain, and diseases of the blood vessels. It is a major cause of death, illness, and productivity loss worldwide. CVD consists of several sub-categories depending on location in the body and pathogenesis, often divided into CVD due to atherosclerosis or due to other causes. CVD caused by atherosclerosis are ischemic heart disease (IHD) for example MI, coronary artery disease, cerebrovascular disease, diseases in major blood vessels including hypertension, or peripheral vascular diseases.

Atherosclerosis is a complex and often time-consuming process occurring in the walls of the blood vessels. Atherosclerosis is caused by an accumulation of fatty materials, cholesterol, and other particles in the blood vessel walls. These accumulations lead to narrowing and irregularities of the inner side of the blood vessels, that later often results in restrictions in blood flow. These accumulations

are prone to rupture, in term leading to possible formations of blood clots. If such a blood clot is developed in a coronary artery, it can lead to a MI, or if it develops in the brain, an ischemic stroke (WHO, 2011).

IHD is a sub-category of CVD; it refers to disturbance of cardiac function due to a relative lack of oxygen in the heart. Most often, this is caused by atherosclerosis (plaque formation and/or rupture leading to a decrease in- or no blood flow) in the coronary arteries. Ischemic stroke is one of the major types of conditions summarised under the umbrella term stroke, the other being haemorrhagic stroke and subaracnoidal haemorrhage. Ischemic stroke is characterised by a loss of blood flow in an artery to/or in the brain.

1.2.1.Risk factors

Numerous risk factors have been implicated in the mechanisms leading up to atherosclerosis related CVD and IHD. For example, socioeconomic status (Sahar & Sassone-Corsi, 2009; Sephton & Spiegel, 2003), gender, lifestyle factors, including elevated body mass index (BMI), and current tobacco smoking, hypertension, and elevated blood cholesterol (Frost et al. 2009) are all well established risk factors for IHD.

Socioeconomic status have been reported to effect both the incidence of ischemic stroke and MI (Peltonen et al. 2000). Hypertension and diabetes (Tuomilehto et al. 2010), sleep apnoea (Yaggi et al. 2005), tobacco smoking (Wolf et al. 1988), are examples of risk factors associated with increased risk of developing ischemic stroke.

1.2.2.Incidence of myocardial infarction and ischemic stroke

In the Nordic countries, national hospital discharge registers can be used to gather data about the incidence of hospitalisation due to IHD, creating unique opportunities in presenting updated statistics (Madsen et al. 2007). The age-adjusted incidence rate of MI in Sweden during 2010 was 677 cases per 100 000 men and 466 cases per 100 000 women. 41 048 cases had incident MI and 38 464 persons were hospitalised due to IHD during 2010 (Socialstyrelsen, 2011a).

The incidence of ischemic stroke in Sweden have been reported to increase, with the incidence for men being around 650 cases per 100 000 men and the corresponding figures for women being 400 cases per 100 000 women (Pessah-Rasmussen et al. 2003). In 2010 in Sweden, the total number of incident cases of ischemic stroke were 21 386 (Socialstyrelsen, 2011a).

1.2.3.Mortality and case fatality

IHD related mortality is decreasing in most European countries but it is still a major cause of death, resulting annually in approximately 740 000 deaths, of which

250 000 occur among people under 75 years of age (Allender et al. 2008). The mortality of MI in Sweden during 2010 were 92 deaths per 100 000 males and 68 deaths per 100 000 women. For ischemic stroke, the mortality in Sweden in 2010 of ischemic stroke were 16 death per 100 000 males and 22 deaths per 100 000 women (Socialstyrelsen, 2011a).

Case fatality can act as an indication of disease severity. A common definition of case fatality is the proportion of cases which are fatal within 28 days after the event (Messner & Lundberg, 2004). In general, men have a higher case fatality of MI than women (MacIntyre et al. 2001). Low socioeconomic status, based on employment type, have been reported to increase case fatality of MI in Sweden (Peltonen et al. 2000).

1.3. Shift work and chronic disease

A growing body of evidence have indicated that shift work may be a risk factor for a number of chronic diseases such as some types of cancer and CVD. Other studies have hypothesised that shift work may be associated with the development of different metabolic disorders, lifestyle factors and different forms of stress (Frost, 2009; Green, Takahashi, & Bass, 2008). Disruption of the human body's daily rhythm, also called the circadian rhythm, has also been proposed to be associated with an increased risk of some cancer types among shift workers (Kolstad, 2008).

The evidence for whether shift work is associated with cancer is not conclusive. Shift work has been assessed as probably carcinogenic to humans due to its disruption to the circadian rhythm (Straif et al. 2007). Overall, there is moderate suggestive evidence for an association between long-term night work (around 20 years) and an increased risk of developing breast cancer (Wang et al. 2011). The same review also concluded that the data on the association with cancers at other sites total cancer incidence were not conclusive (Wang et al. 2011).

1.3.1. Shift work and association with the metabolic syndrome and diabetes type II

Metabolic syndrome is the name of a cluster of risk factors; central obesity, hypertension, elevated triglycerides, lowered high density lipoprotein (HDL) cholesterol and elevated fasting glucose, often seen simultaneously (Alberti et al. 2009). Most of the published data support an adverse association between shift work and the risk of developing metabolic syndrome (De Bacquer et al. 2009; Karlsson, Knutsson, & Lindahl, 2001; Lin, Hsiao, & Chen, 2009; Pietroiusti et al. 2010; Sookoian et al. 2007). However, one study found no increased association between night shift workers and day workers and the risk of metabolic syndrome (Violanti et al. 2009). A recent review covering the subject concluded that the evidence for an adverse association between shift work and the metabolic syndrome was moderate (Wang et al. 2011).

Shift work has been hypothesised to be associated with an increased incidence of diabetes type II; however, evidence from epidemiological studies is limited (Kawakami et al. 1999; Kroenke et al. 2007; Nagaya et al. 2002). In 2005, Karlsson and co-workers reported that the number of years of shift work was associated with increased risk of mortality with diabetes type II as an underlying or contributory cause, although none of the reported results were statistically significant (Karlsson et al. 2005). While several studies have found a strong association, others have not (Morikawa et al. 2005). The evidence for an adverse association between shift work and diabetes type II was reported as limited in the review by Wang and co-workers (2011) (Wang et al. 2011).

1.3.2. Shift work and association with cardiovascular disease

A growing body of evidence have studied the association between shift work and CVD, the major part with positive findings. Alfredsson and co-workers (1982) analysed MI in a case-control study of 1 216 participants, rendering a relative risk of 1.25 (95% confidence interval (CI) 0.97–1.62) (Alfredsson et al. 1982). Koller (1983) did a descriptive study that analysed a selection of health outcomes among 1 260 male participants. They reported that the prevalence of diseases of the circulatory system were 2.7 times more common among shift workers compared to day workers (Koller, 1983). Falger and Schouten (1992) did a case-control study analysing MI incidence among workers with prolonged or irregular working hours or shift work. They reported an OR of 1.16 (95% CI 0.68-2.0) for the 458 participants (Falger & Schouten, 1992). Bøggild and co-workers (1999) used a prospective cohort design comprising 5 249 participants using IHD and all-cause mortality as the outcome variable. They reported a relative risk of IHD related to shift work of 1.0 (95% CI 0.9-1.2)(Bøggild et al. 1999).

Vertin (1978) analysed the incidence of CVD in a combined case-control and cohort study of 300 participants and reported that they did not find any risks associated with shift work (Vertin, 1978). Alfredsson and co-workers (1985) followed 958 069 participants in a retrospective cohort study analysing hospitalisation for MI. They reported that the standardised mortality ratio for exposure to irregular working hours to be 115 (95% CI 104-126) for men and 152 (95% CI 119-191) for women (Alfredsson, Spetz, & Theorell, 1985). Knutsson and co-workers (1986) used a prospective cohort design, where 504 participants were followed using IHD as the main outcome variable. Their main findings was that the relative risk after 11-15 years of shift work was 2.2 and after 16-20 years it was 2.8 (Knutsson et al. 1986). In 1999, Knutsson and co-workers (1999) did a case-control study comprising 4 648 participants; the study was focused at analysing increased risk of MI among shift workers. They found that shift work was associated with an increased risk of MI (OR), 1.3 (95% CI 1.1 to 1.6) for men and 1.3 (95% CI 0.9 to 1.8) (Knutsson et al. 1999).

In 2007, Ellingsen and co-workers did a cohort study that comprised 2 598 participants, with the aim of analysing the association between shift work and incidence of CHD. They reported that the relative risk of cardiovascular events among shift workers was 1.65 (95% CI 1.38–1.97) (Ellingsen, Bener, & Gehani, 2007). Haupt and co-workers (2008) used data from a cross-sectional survey to analyse if shift work was associated with atherosclerosis and MI, among 3 208 participants. They found that shift work was associated with atherosclerosis and that the hazard ratio for younger shift workers risk of MI was 1.53 (95% CI 1.06–2.22) (Haupt et al. 2008).

The possibly adverse effect of shift work on the cardiovascular system was highlighted in an early review that included studies on fatal events and studies combining fatal and non-fatal events and one study that separated the two (Åkerstedt et al. 1984). A later review estimated that shift workers had a 40% increased risk of CVD (Kristensen, 1989), the same conclusion was put forward about 10 years later in another review (Bøggild & Knutsson, 1999). Another review, that included studies using either fatal, combined fatal and non-fatal or separated fatal and non-fatal events as outcome variable, concluded that the epidemiological evidence for a causal association between shift work and IHD was limited. However, the same review could be viewed as rather restrictive in its judgement of the results in the included studies (Frost et al. 2009). A more recent review concluded that there were moderate support for the adverse association between shift work and CVD (Wang et al. 2011). In comparison to some of the other recent reviews on this issue, this was somewhat more transparent in its grading of their findings by the fact that they were using Royal College of General Practitioners three-star system (Wang et al. 2011).

A meta-analysis from 2012 that comprised just over two million people concluded that shift work was associated with MI (risk ratio 1.23 with 95% CI 1.15-1.33), and ischemic stroke (1.05 95% CI 1.01-1.09). It also concluded that shift work was associated with coronary events (risk ratio of 1.24 95% CI 1.10-1.39) (Vyas et al. 2012). The same study had rather generous inclusions criteria, resulting in an analysis conducted on an extensive body of evidence. They included studies that usually do not appear in the discussion on the association between shift work and CVD (Vyas et al. 2012). In their generous inclusion criteria, there is a risk of underestimating the association between shift work and CVD. Some of the articles they include have made exposure assessments that potentially confounds the effect of the exposure, or not reporting how the exposure was assessed, for example just using type of employment as a proxy for the exposure. The issue of study quality in early studies on shift work and CVD has been addressed previously (Kristensen, 1989).

1.3.3. Shift work and ischemic stroke

Two studies have analysed the association between shift work and incidence of ischemic stroke, and one study has analysed the association with ischemic stroke mortality. The first study analysed shift work and ischemic stroke mortality in a retrospective cohort of 5 442 participants. That study reported that the standardised relative rates for shift workers ischemic stroke mortality was 1.56 (95 % CI 0.98-2.51) (Karlsson et al. 2005). The other study that did not find any association between the incidence of ischemic stroke and shift work was a case-control study of 607 participants and reported an odds ratio (OR) of 1.0 (95% CI 0.6-1.8) (Hermansson et al. 2007).

While some studies found no association, one study found an association with ischemic stroke and shift work (Brown et al. 2009). In their analysis, they included only female nurses working rotating shift with night shifts in their analysis. The study was based on a prospective cohort comprising just over 80 000 participants. They reported a hazard ratio of 1.04 (95% CI 1.01–1.07), of ischemic stroke for every five years of rotating night shift work (Brown et al. 2009).

The data from the two studies on ischemic stroke incidence and shift work were compiled in a recent meta-analysis resulting in a risk ratio of 1.05 (95% CI 1.01-1.09) (Vyas et al. 2012).

1.4. Shift work and mortality from coronary heart disease, stroke and all-cause mortality

A handful of studies have analysed if CVD mortality is greater for shift workers compared to day workers. Rafnarsson and Gunnarsdottir (1990) found, in their retrospective cohort study of 603 participants, that the standardised mortality ratio for coronary mortality was 121 for all participants and 102 for participants that worked shift for over 15 years (Rafnsson & Gunnarsdóttir, 1990). Kawachi and co-workers (1995) did a prospective cohort study that comprised 79 109 female nurses, they reported a relative risk of CHD of 1.38 (95% CI, 1.08-1.76) (Kawachi et al. 1995). Fujino and co-workers (2006) followed 17 649 male industrial workers in a prospective cohort study. They found that shift workers had an increased risk of IHD mortality compared to day workers (relative risk 2.32, 95% CI 1.37-3.95) (Fujino et al. 2006). Another study followed 23 257 participants with a focus on all-cause mortality and found a hazard ratio of 2.61 (95% CI 1.26-5.41) for female white-collar shift workers as the only significant finding (Åkerstedt, Kecklund, & Johansson, 2004).

A number of other studies did not find any support for the association, they reported risk estimates ranging from 0.64 to 1.11 (Karlsson et al., 2005; McNamee et al. 1996; Steenland & Fine, 1996; Tarumi, 1997; Taylor & Pocock, 1972; Virtanen & Notkola, 2002; Yadegarfar & McNamee, 2008). Taylor and Pocock (1972) reported a

standardised mortality ratio of 1.03 for shift workers among their 8 603 study participants (Taylor & Pocock, 1972). That study was re-analysed in 2004 with the following results reported, an overall mortality risk of former and current shift workers of 1.05 (95% CI 0.95-1.16). The same study also reported that shift workers aged 45-54 had a relative risk of 1.47 in all cause mortality (95% CI 1.12-1.93) (Knutsson, Hammar, & Karlsson, 2004). McNamee and co-workers (1995) reported an OR of 0.90 (90% CI 0.68–1.21) among their 934 participants for coronary mortality (McNamee et al. 1996). Steenland and Fine (1996) reported an OR of 0.64 (95% CI 0.28–1.47) in 21 491 study participants (Steenland & Fine, 1996).

In their retrospective cohort study comprising over 385 000 participants, Virtanen and Notkola (2002) reported that they did found a relative risk of increased mortality related to shift work to be non-significant (Virtanen & Notkola, 2002). In the retrospective cohort study made by Tarumi (1997) analysing the overall mortality of 19 642 participants concluded that the OR for shift workers was 0.96 (95% CI 0.59-1.56) (Tarumi, 1997).

Another study reported a standardised relative risk of 1.24 (95% CI 1.04-1.49) among shift workers with at least 30 years of shift work exposure (Karlsson et al. 2005). The study by Yadegafar and McNamee (2008) used a case-control design with coronary mortality as outcome variable. They reported an OR of 1.03 (90% CI 0.83–1.28) (Yadegarfar & McNamee, 2008). In 2012, Hublin and co-workers followed a cohort of 20 142 participants analysing if shift work was associated with CHD mortality. The hazard ratio for CHD mortality in relation to shift work was 1.09 (95% CI 0.82, 1.44) for men and 1.22 (95% CI 0.83, 1.79) for women (Hublin et al. 2010).

A recent meta-analysis reported that shift work was not associated with increased rates of all-cause or vascular specific mortality (Vyas et al. 2012).

Studies based on death certificates have well-known limitations. One limitation is ill-defined cause of death, especially among elderly persons. The frequency of autopsy is very low in Sweden, 7% in female and 16% in males (Socialstyrelsen, 2011b). All this may result in physicians having insufficient information about the patient.

1.5. Shift work and health disorders

Besides being associated with a number of severe chronic diseases, shift work is also associated with a number of health disorders; the ones being immediate are gastrointestinal malfunction, sleep disturbance, and fatigue. Such symptoms often start soon after starting to work shift work in susceptible individuals (Knutsson & Bøggild, 2010).

Common symptoms of gastrointestinal malfunction among shift workers are pain or altered bowel movements manifested as either constipation or diarrhea. Shift work is also associated with peptic ulcer. The same review also concluded that shift work is likely to be associated with adverse pregnancy outcomes such as miscarriage, low birth weight, and preterm birth (Knutsson, 2003).

Shift work is associated with adverse effects on sleep, performance, and risk of accidents (Åkerstedt & Wright, 2009). Around two thirds of shift workers are affected by disturbed sleep (Åkerstedt, 1988) making it one of the most frequently reported health disorder among shift workers (Åkerstedt & Wright, 2009).

1.6. Potential mechanisms explaining increased risk of chronic disease and health disorders associated with shift work

Many biological variables exhibit a circadian rhythm, a rhythm that can be disrupted by shift work. The circadian rhythm in humans is governed by the master clock in the suprachiasmatic nucleus in the hypothalamus in the brain. From there, signals transmit to the pineal gland and stimulate production and secretion of the hormone melatonin to the blood. Melatonin in turn influences the secretion of cortisol and other hormones affecting the circadian body rhythm including sleep.

Circadian disruption and stress related to interference with the normal metabolic and hormonal functions are examples of proposed pathways linking shift work to CVD and other chronic conditions (Green et al. 2008). Circadian disruption related to shift work has been shown to adversely affect blood lipids and blood pressure and is thereby likely to increase the risk of CVD (De Bacquer et al. 2009). Moreover, the increased prevalence among shift workers of for example tobacco smoking and unhealthy dietary patterns may also be linked to the increased risk of developing CVD (Zhao & Turner, 2008). It has also been proven, using ultrasonic measures, that shift work is associated with subclinical atherosclerosis (Haupt et al. 2008).

1.7. Summary

There is some evidence supporting the association between shift work and increased risks of CVD and other severe diseases. There may be a number of mechanisms involved in these associations, such as sleep disturbance and associated lifestyle factors, however more research is needed to establish the contribution of these mechanisms.

2. AIM AND OBJECTIVES

The aim of this thesis was to further study the proposed association between shift work and CVD. This was done by focusing on the following objectives:

- Do shift workers have an increased risk of ischemic stroke compared to day workers?
- Do shift workers have an increased risk of case fatality after a MI compared to day workers?

3. METHODS

3.1. Study populations

The following chapter gives a description of the study populations and analytical approaches utilised in the two studies.

3.1.1. MONICA/VIP (paper I)

This was a nested case–control study consisting of the Northern Sweden Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) study and the Västerbotten Intervention Programme (VIP). This MONICA study started in 1985 in two counties in northern Sweden, Västerbotten and Norrbotten. VIP is an on-going intervention program focusing on prevention of CVD and diabetes type II in Västerbotten County in Sweden. From January 1 1985 to September 30 2000, about 66 300 individuals had participated in the VIP or MONICA health surveys.

Case findings were based on reports from hospitals and general practitioners, screening of hospital discharge registers and all death certificates. In fatal cases, the data from death certificates and from necropsy reports were used to complete the diagnosis (Stegmayr & Asplund, 2003).

The diagnosis of ischemic stroke was based on the definition from the International Classification of Diseases, ninth revision as follows: brain infarction or ischemic stroke (ICD 434) and no signs of hemorrhage in a CT scan or at necropsy. Only cases classified as definite events were included as non-fatal cases. In fatal events, possible infarction and unclassified infarction were included (Stegmayr, Asplund, & Wester, 1994). For each case, five matched controls without known CVD and cancer were selected from the MONICA and VIP cohorts.

The material analysed in paper I consisted of 138 shift workers and 469 day workers. The analysis included 194 cases, of which 44 cases were shift workers.

Exposure information

Additional data used in the analyses were gathered from health examinations and questionnaire data. The shift work variable was based on the responses to two questions from the population survey. Current tobacco smoking, work related stress measured with the job strain concept, hypertension, high triglycerides and high cholesterol and low social status (estimated using low educational level) were analysed as potential covariates.

3.1.2. SHEEP/VHEEP (paper II)

Cases were defined as all first episodes of non-fatal and fatal first events of MI, and were collected from a case-referent database that consisted of two parallel studies: the Stockholm Heart Epidemiology Programme (SHEEP), and the Västernorrland Heart Epidemiology Program (VHEEP). The combined study base of the two studies contained all Swedish citizens living in the counties of Stockholm or Västernorrland in Sweden, who were free of previously diagnosed MI.

Cases were included at the time of incidence of MI. They were identified from (*a*) the coronary and intensive care units at the internal medicine departments at all the emergency hospitals within the counties of Stockholm and Västernorrland, (*b*) the hospital discharge register for the same counties, and (*c*) death certificates from the National Register of Causes of Death at Statistics Sweden. The criteria of diagnosis included (*a*) certain symptoms according to information on case history, (*b*) specified changes in blood concentrations of the enzymes creatine kinase and lactate dehydrogenase, (*c*) specified electrocardiographic changes, and (*d*) necropsy findings. The diagnosis of MI required two of the criteria *a–c* to be met, or that necropsy findings showed myocardial necrosis of an age compatible with the time of onset of the disease. A small group of cardiologists assessed the medical inclusion and exclusion criteria for the cases in hospital; thus, the same diagnostic criteria were applied for all cases in hospital.

Cases were the patient died before admission to hospital were identified via special routines at the Statistics Sweden. Cases with previous hospital admissions for MI were excluded from the study base. Non-fatal cases answered a questionnaire as soon as possible after recovering. For fatale cases, questionnaire information was obtained from a close relative three to 6 months after the occurrence of MI.

The material used in the analysis in paper II consisted of 1 542 cases of MI and with complete working schedule information. Among male MI-cases, 210 were shift workers and 937 were day workers. Among females, the corresponding numbers were 69 and 326. To reduce the risk of including participants that were retired, the

age limit for inclusion in the analysis was set to 65 years and unemployed or retired cases were excluded.

Case fatality in this study was the proportion of cases with first time MI consistent with the previously described criteria, which were fatal within 28 days after the event. The participants had a mean age of 57.1 (SD 5.8, median 58) years.

Exposure information

Shift work exposure and prevalence of covariates such as low level of spare time physical activity, current tobacco smoking, BMI ≥ 28, diabetes type II, low socioeconomic status, hypertension, and job strain were assessed through questionnaire data.

3.2. Statistical methods

All calculations were made separately for men and for women. For the covariates, the differences between shift- and day workers were analysed with chi-square tests or independent samples t-test depending on the type of data. A p-value of <0.05 was considered statistically significant. To determine the risk of shift workers developing ischemic stroke or risk of case fatality, logistic regressions to calculate OR with 95% CI were used.

In study I and II, multiple adjustments were made separately for potential confounders of behavioural or medical origin.

All of the statistical calculations were carried out using the statistical software SPSS 12.0 for paper I, and SPSS 16.0 for paper II (SPSS Inc. Chicago, IL, USA).

4. RESULTS

4.1. Shift work and ischemic stroke (paper I)

No statistically significant differences were found between the day and shift workers regarding the prevalence of the assessed risk factors (results presented in detail in paper I).

Table 1: Age-adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for shift work in comparison with day work and the risk of ischemic stroke, with adjustment for different covariates — results of logistic regression analysis.

	Men		Women	
Model 1	**OR**	**95% CI**	**OR**	**95% CI**
Shift work [a]	1.0	0.6-1.8	1.0	0.6-1.8
Shift work, adjusted for job strain	1.3	0.7-2.3	1.0	0.5-1.9
Shift work, adjusted for smoking	1.0	0.6-1.8	1.1	0.6-2.0
Shift work, adjusted for low educational level	1.0	0.6-1.9	1.1	0.6-2.0
Shift work, adjusted for job strain, smoking, low educational level	1.2	0.6-2.3	1.0	0.6-2.0
Model 2				
Shift work [a]	1.0	0.6-1.8	1.0	0.6-1.8
Shift work, adjusted for high triglycerides	1.0	0.5-2.0	1.0	0.5-1.9
Shift work, adjusted for high total cholesterol	1.0	0.5-1.8	0.9	0.5-1.6
Shift work, adjusted for hypertension	0.9	0.5-1.8	0.6	0.3-1.2
Shift work, adjusted for high triglycerides, high total cholesterol, hypertension	1.1	0.5-2.2	0.9	0.4-1.7

[a] Crude OR

The results of the logistic regressions, displayed in table 1, did show small but non-significant differences between day- and shift workers and the risk for ischemic stroke. In model 1, adjusting the OR for behavioural related covariates, none of the regressions indicated any significant associations between shift work and ischemic stroke. The same results were found in model 2 that adjusted for medical covariates.

4.2. Shift work and case fatality (paper II)

There were marked differences between day- and shift workers regarding current tobacco smoking, BMI above 28, low socioeconomic status and job strain for both men and women. Physical inactivity and diagnosed diabetes type II were more common among male shift workers compared to male day workers; no such difference was seen for women. No other major differences were found (results presented in detail in paper II).

The percentage of male shift workers who died of MI within 28 days (case fatality) after the event was 21.2% of 210 cases, compared to 14.3% of 937 cases among day workers. The corresponding figures for females were 13% of 69 cases of MI among shift workers compared to 21.2% of 326 cases among day workers.

Table 2: Age-adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for shift work in comparison with day work and risk of 28-day case fatality of myocardial infarction, with adjustment for different covariates — results of logistic regression analysis.

	Men		Women	
	OR	**95% CI**	**OR**	**95% CI**
Shift work [a]	1.6	1.1-2.4	0.6	0.3-1.2
Shift work, adjusted for physical inactivity	1.6	1.1-2.3	0.7	0.3-1.4
Shift work, adjusted for current tobacco smoking	1.7	1.1-2.4	0.6	0.3-1.2
Shift work, adjusted for BMI ≥ 28	1.6	1.1-2.4	0.4	0.2-1.1
Shift work, adjusted for diabetes type II	1.7	1.1-2.4	0.6	0.3-1.2
Shift work, adjusted for low socioeconomic status	1.4	0.8-2.3	0.3	0.1-1.1
Shift work, adjusted for hypertension	1.8	1.2-2.7	0.5	0.2-1.1
Shift work, adjusted for job strain	1.6	1.1-2.4	0.4	0.2-1.0
Shift work, adjusted for BMI ≥ 28, diabetes type II and hypertension	2.2	1.5-3.2	0.5	0.2-1.4
Shift work, adjusted for physical inactivity, current tobacco smoking, low socioeconomic status and job strain	1.7	1.1-2.6	0.4	0.1-1.3

[a] Crude OR

As displayed in table 2, the crude OR for case fatality following an MI for male shift workers was 1.6. Adjustments for potential risk factors yielded minor changes

in the OR except for low socioeconomic status that rendered some change but to a non-significant result. When combining exposure to elevated BMI, diabetes type II and hypertension in a multivariate regressing model in order to analyse the associations related to medical risk factors, the OR for male shift workers was 2.2. In the other multivariate regression model, combining risk factors more directly associated with behavioural and social factors, the OR from male shift workers was relatively constant compared to previous results.

The OR for female shift workers was 0.6, however non-significant. Adjustment for selected covariates in both univariate and multivariate regression models did not yield any significant results for female shift workers.

Socioeconomic status was also analysed using other analytical approaches, all yielding non-significant results (results not presented in this thesis). Other regression models including participants over 65 years of age were also preformed. The results were largely similar to those presented using only participants under 65, except for the OR for male shift workers that was around 20% lower (results not presented in this thesis).

5. DISCUSSION

In summary, the results of this thesis did not show any associations between shift work and the risk of ischemic stroke. The result did show an elevated risk of case fatality after MI for male shift workers, no such results were found for female shift workers.

5.1. Shift work and ischemic stroke (paper I)

The results from paper I showed that shift workers did not have an increased risk of ischemic stroke compared to day workers. The findings contradict the findings of other study that analysed the same hypothesis (Brown et al. 2009).

Tüchsen analysed stroke morbidity for Danish drivers (Tüchsen, 1997), but did not make any specific analyses regarding the effects of shift work but claimed that there may be a possible connection between stroke and shift work. There were some differences between the studies reporting positive or negative results on the association in question. One major difference was that one study only analysed nurses working night shift (Brown et al. 2009). Among the studies that did not find any association, both were using rather small study samples and in one case, the outcome was ischemic stroke mortality (Hermansson et al. 2007; Karlsson et al. 2005).

It is possible to assume that shift work may affect the risk of ischemic stroke, supported by the results in Vyas and co-workers (2012) that reported a potential increased risk of 5% (Vyas et al. 2012). That study only used the two available studies analysing ischemic stroke and its association to shift work (Brown et al. 2009, Hermansson et al. 2007). By doing so, they excluded the broader definition cerebrovascular disease occurring as outcome foremost in mortality studies, probably preferable because of the different type of mechanisms leading up to cerebrovascular disease and mortality are more wide-spread than the ones leading up to ischemic stroke.

One circumstance that could have influenced the results in paper I was the fact that about 80% of all cases of ischemic stroke usually occur after 65 years of age, and most of the participants included in the analysis were under that age. Because the official retirement age in Sweden is 65 years, it would be possible to assume that the incidence would have been higher if the age span had been greater. However, in an analysis considering that possibility, the shift work variable would lose some of its validity because most of the participants would be retired and therefore no longer directly exposed to shift work.

5.2. Shift work and case fatality (paper II)

The analysis in paper II showed an increased risk of death within 28 days after MI for male shift workers. When adjusting for selected covariates in different regression models, the OR changed marginally. No such risk increase was found for female shift workers.

After adjusting for physical inactivity, the OR decreased slightly for male shift workers. This result may be explained by the fact that the prevalence of physical inactivity was higher among shift workers. Adjusting for current tobacco smoking, BMI ≥ 28, diabetes type II, socioeconomic status, or job strain did not change the OR to any greater extent.

Adjusting for hypertension for male shift workers gave the most marked increase in OR for case fatality for male shift workers. Elevated blood lipids (cholesterol and triglycerides) and hypertension were not assessed in this analysis due to lack of such data for cases included in the data set.

In the studies analysing CVD-mortality and shift work, there were a few points that need further attention. Given that many of the study populations were different in their composure, e.g. gender, occupational exposure, the selected outcome variables e.g. IHD compared to CVD could potentially have contributed to mixture of positive and negative associations between shift work and CVD-related mortality.

Moreover, there is a mixture of exposure comparators and exposure assessments in the previous studies analysing shift work and CVD mortality. Some studies compare shift or night workers against the general population or against non-shift or day workers. When assessing the risks attributable to shift work, it is likely that day workers are the preferred comparator, for example because their working status will be associated with a higher validity.

In addition, there may be a need to further development in the granularity of the shift work exposure. By just using a one-dimensional shift work variable, the information about the length of shift work exposure will be excluded from the analysis. That may underestimate a potential dose-response effect in the length of shift work exposure.

Of the studies investigating CVD mortality among shift workers, the size of the study populations did not seem to affect the outcome results. Another aspect in need of further attention is confounding control. It is vital to control for confounding factors known to be more prevalent among shift workers than day workers such as tobacco smoking. If not performed, there is a risk of falsely estimating the risk associated with shift work exposure. Moreover, a large quantity of the studies included in the meta-analysis addressed the issue of adjusting their analyses for potential covariates when so possible, indicating an understanding of their potential effects on the outcome (Vyas et al. 2012). The same study also reported that shift work was not associated with increased rates of all-cause or vascular specific mortality (Vyas et al. 2012).

If, as in the case in paper II for male shift workers, the case fatality of MI is elevated, it is likely to have an effect on the total mortality, however not to an extent that results in significant risk increase. This will warrant caution of MI cases with shift work exposure that in term can reduce the overall CVD mortality and act as a foundation for prevention of case fatality.

5.3. Study design considerations

Both paper I and II were based on case-control studies, conducted by well-established research organisations, thereby accounting for a presumably good data quality and thereby positively affecting the precision in the received results.

There is a potential risk of misclassification related to the use of questionnaire data for fatal cases submitted by a close relative, primarily due to recall bias. This fact might influence the result to some extent, but the level of impact on the results remains hypothetical.

The definition of shift work in this study was based on questionnaire data. Respondents who reported having day work might in fact be former shift workers

and vice versa. There is also a risk of respondents having trouble in correctly determining their working conditions. This may perhaps lead to an underestimation of the risk of the shift work exposure. The fact that the question used does not take into account the period during which the present working conditions have existed also represents a risk of misclassifications.

5.4. Interpretation and implications

Shift work did not seem to be associated with an increased risk of ischemic stroke. Thereby, it is likely to assume that the increased adverse association between CVD and shift work is less associated with ischemic stroke and more likely with CHD. This is supported by the increased risk of ischemic stroke of 5% for shift workers reported in a recent meta-analysis (Vyas et al. 2012).

Exposure to shift work could be associated with increased risk of death within 28 days after MI for male shift worker. This finding may warrant increased caution of male shift workers presenting with MI, also this may call for more life style preventive measures to counteract sedentary life style among shift workers. Such efforts may decrease suffering, MI mortality, and result in health improvements.

Given that shift work is common in the modern society, efforts in primary and secondary prevention aimed at improving health and preventing disease among shift workers is of major societal concern.

5.5. Need for further study

The findings of this thesis bring further understanding of the potential associations between shift work and CVD. However, much remains to be investigated, future research priorities may include:

- Prospective cohort studies of shift workers and non-shift workers with clarified disease end-points, to bring more light to the association between shift work and CVD
- Most of the research conducted on shift work have been performed on a limited number of occupational groups, thereby research on a wider variety of occupational groups is needed
- More research on potential biological mechanisms is needed to bring more understanding to their effects on the association between shift work and CVD, especially with a focus on the association between shift work and the development of atherosclerosis
- There is a great need of further understanding of the gender differences in both risk of outcomes and regarding shift work exposure assessment
- Increased use of a more granular assessment of shift work exposure may lead to less heterogeneity in the results; the same goes for a harmonisation of the analysed CVD outcome variables

- There would also be of interest to explore whether there exists a greater recall bias related to whether one has been exposed to shift work or night work

6. CONCLUSION

In summary, the findings did not indicate a higher risk of shift workers developing ischemic stroke compared to day workers. The risk was consistent despite the introduction of several recognised risk factors for ischemic stroke.

The findings also showed that male shift workers tended to have an increased risk for case fatality within 28 days after MI, such results were not found for female shift workers. In the existing literature, no other studies were found that analysed case fatality of MI for shift workers. Therefore, the findings of this study are to be regarded as preliminary and more research in the field is needed.

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