Thesis for the degree of Doctoral, Sundsvall 2015

SHIFT WORK AND CARDIOVASCULAR DISEASE

Jonas Hermansson

Supervisors:
Katja Gillander Gådin, Anders Knutsson and Berndt Karlsson

Department of Health Sciences
Mid Sweden University, SE-851 70 Sundsvall, Sweden

ISSN 1652-893X,
Mid Sweden University Doctoral Thesis 231
ISBN 978-91-88025-41-8
SHIFT WORK AND CARDIOVASCULAR DISEASE
Jonas Hermansson

© Jonas Hermansson, 2015

Department of Health Sciences, Faculty of Human Sciences
Mid Sweden University, SE-851 70 Sundsvall
Sweden

Telephone: +46 (0) 10 142 80 00

Printed by Kopieringen Mid Sweden University, Sundsvall, Sweden, 2015
To my relief.
ABSTRACT
Shift work is often defined as working time outside daytime hours (06:00 to 18:00). In recent years, shift work has been associated with an increased risk of cardiovascular disease (CVD), type II diabetes, and the metabolic syndrome. While some studies support the associations, others do not. Therefore, more research is needed. The aim of this thesis was to further study the association between shift work and CVD. This was addressed by performing four studies, one analysed if shift workers had an increased risk of ischemic stroke, the second study analysed whether shift workers had an increased risk of short-term mortality (case fatality) after a myocardial infarction (MI). The third study analysed if shift work interacts with other risk factors for MI and the fourth study analysed if paternal history of CVD interacted with shift work on the risk of MI. The studies were performed using logistic regression analyses and additive interaction analyses in two different case-control databases.

Shift workers did not have an increased risk of ischemic stroke. Male shift workers had an increased risk of death within 28 days after a MI. Shift work interacts with some CVD risk factors and interacts with paternal history of CVD and the risk of MI for males. The findings from this thesis provide new evidence showing that shift work is in different ways associated with an increased risk of MI and related mortality, but not with ischemic stroke. However, more research is needed to clarify and characterise these results.

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


Nyckelord: Skiftarbete, epidemiologi, hjärt-kärlsjukdomar, stroke, mortalitet
LIST OF PAPERS

This thesis is mainly based on the following 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.

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

Paper III Interaction between shift work and coronary risk factors on risk of myocardial infarction.
In manuscript.

Paper IV Interaction between parental history of myocardial infarction or sudden cardiac death and shift work on the incidence of myocardial infarction among males.
Hermansson, J., Karlsson, B., Knutsson, A., & Gillander Gådin, K.
In manuscript.

Paper I is published with the kind permission of the editor in chief of Scandinavian Journal of Work Environment & Health. Paper II is published with the kind permission of Springer Science and Business Media.
<table>
<thead>
<tr>
<th>TABLE OF CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABBREVIATIONS</td>
</tr>
<tr>
<td>INTRODUCTION</td>
</tr>
<tr>
<td>SHIFT WORK</td>
</tr>
<tr>
<td>SHIFT WORK AND HEALTH DISORDERS</td>
</tr>
<tr>
<td>Shift work and the metabolic syndrome and diabetes type II</td>
</tr>
<tr>
<td>CARDIOVASCULAR DISEASE</td>
</tr>
<tr>
<td>Ischemic heart disease and stroke</td>
</tr>
<tr>
<td>Risk factors</td>
</tr>
<tr>
<td>Modifiable risk factors</td>
</tr>
<tr>
<td>Non-modifiable risk factors</td>
</tr>
<tr>
<td>Other types cardiovascular disease</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
</tr>
<tr>
<td>Artery disease</td>
</tr>
<tr>
<td>SHIFT WORK AND MORBIDITY OF CORONARY HEART DISEASE</td>
</tr>
<tr>
<td>SHIFT WORK AND CARDIOVASCULAR DISEASE MORTALITY</td>
</tr>
<tr>
<td>SHIFT WORK AND RISK FACTOR INTERACTION</td>
</tr>
<tr>
<td>SHIFT WORK AND PARENTAL HISTORY OF CARDIOMETABOLIC DISEASE</td>
</tr>
<tr>
<td>SHIFT WORK AND ISCHEMIC STROKE</td>
</tr>
<tr>
<td>POTENTIAL MECHANISMS AFFECTING CARDIOVASCULAR DISEASE AND SHIFT WORK</td>
</tr>
<tr>
<td>Circadian disruption</td>
</tr>
<tr>
<td>Metabolic disturbance</td>
</tr>
<tr>
<td>Life style factors and stress</td>
</tr>
<tr>
<td>Cardiovascular effects</td>
</tr>
<tr>
<td>SUMMARY</td>
</tr>
<tr>
<td>AIM AND OBJECTIVES</td>
</tr>
<tr>
<td>METHODS</td>
</tr>
<tr>
<td>STUDY POPULATIONS</td>
</tr>
<tr>
<td>MONICA/VIP (paper I)</td>
</tr>
<tr>
<td>SLEEPHEEP (paper II, III, and IV)</td>
</tr>
<tr>
<td>Exposure information</td>
</tr>
<tr>
<td>STATISTICAL METHODS</td>
</tr>
<tr>
<td>Interaction on an additive scale</td>
</tr>
<tr>
<td>ETHICAL CONSIDERATIONS</td>
</tr>
<tr>
<td>RESULTS</td>
</tr>
<tr>
<td>SHIFT WORK AND ISCHEMIC STROKE (PAPER I)</td>
</tr>
<tr>
<td>SHIFT WORK AND CASE FATALITY OF MYOCARDIAL INFARCTION (PAPER II)</td>
</tr>
</tbody>
</table>
ABBREVIATIONS

AF atrial fibrillation
AP attributable proportion
AV-node atrioventricular node
BMI body mass index
CI confidence interval
CHD coronary heart disease
CRP C-reactive protein
CT computed tomography
CVD cardiovascular disease
HDL high density lipoprotein
HR hazard ratio
HRV heart rate variability
ICD international classification of diseases
IHD ischemic heart disease
ILO international labour office
LDL low-density lipoprotein
mmHg millimetre mercury
mmol/L millimole per litre
MI myocardial infarction
OR odds ratio
PAD peripheral artery disease
PAR population attributable risk
RERI relative excess risk due to interaction
RR relative risk
SCD sudden cardiac death
SI synergy index
QT time between start of Q wave to end of T wave in the electrical cycle of the heart
WHR waist hip ratio
INTRODUCTION

The working life of today is characterised by a continuous development towards the so-called 24-h society where more and more stores, industries, and service functions are increasing their accessibility. In this process, more and more people are starting to work outside what usually is defined as day work. However, this is not without health consequences (Rajaratnam and Arendt 2001).

A number of studies have shown that shift work is associated with coronary heart disease (CHD) (Vyas et al. 2012), but the evidence on a causal relationship is limited. CHD and ischemic stroke have many common risk factors (Anand et al. 2008; O'Donnell et al. 2010), risk factors that to some extent have been associated with shift work (Bøggild and Knutsson 1999). 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 further the association between shift work and CVD with a focus on ischemic stroke, case fatality among shift workers with myocardial infarction (MI), interaction between CVD risk factors, and parental history of CVD and shift work and the association with MI.

Shift work

Shift work is a term used to define a work schedule being the opposite of daytime work. The International Labour Office (ILO), defines shift work as a “method of organisation of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers” (ILO 2004). This results in different type of work schedules being characterised as shift work such as non-standard, non-regularly occurring working hours, and night work.
An estimated 20% of the European working population are involved in shift work, working time outside day work hours of 06:00 to 18:00 (Parent-Thirion et al. 2007). Shift work is more prevalent in industrial production, hotels, restaurants, transport, and health care (Parent-Thirion et al. 2007; Parent-Thirion et al. 2011). The prevalence of shift work in Sweden is likely to be above 20%, depending on variations in the definition of shift work (Kecklund et al. 2010).

**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; like gastrointestinal malfunction, sleep disturbance, and fatigue. Such symptoms often start soon after starting to work shift work in susceptible individuals (Knutsson and Bøggild 2010). Common symptoms of gastrointestinal malfunction among shift workers are pain or altered bowel movements manifested as either constipation or diarrhoea. Shift work is also associated with peptic ulcer. 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 and Wright 2009) and cognition impairments (Marquie et al. 2015). 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 and Wright 2009).

Shift work has also been associated with an increased risk of foremost breast cancer. There are moderate support for an association between long-term night work (around 20 years) and an increased risk of developing breast cancer. The data

---

1 The sixth European Working Conditions Survey is being performed during 2015, with results expected in the end of 2015.
on the association with cancers at other sites in the body and total cancer incidence with shift work were not conclusive (X. S. Wang et al. 2011).

**Shift work and the metabolic syndrome and diabetes type II**

Shift work is associated with the development of different metabolic disorders, lifestyle factors, and different forms of stress (Frost et al. 2009; Green et al. 2008).

Metabolic syndrome is a cluster of risk factors; central obesity, high blood pressure, elevated triglycerides, lowered high density lipoprotein (HDL) cholesterol and elevated fasting glucose, often seen simultaneously (Alberti et al. 2009). Most of the studies support an association between shift work and the metabolic syndrome (De Bacquer et al. 2009; Karlsson et al. 2001; Lin et al. 2009b, 2009a; Pietroiusti et al. 2010; Sookoian et al. 2007). However, one study found no increased association between night shift work and the association with the metabolic syndrome (Violanti et al. 2009). A review from 2011 covering the subject concluded that the evidence for an association between shift work and the metabolic syndrome was moderate (X. S. Wang et al. 2011). A meta-analysis from 2014 concluded that night shift work was associated with the metabolic syndrome (F. Wang et al. 2014).

Shift work is associated with an increased incidence of diabetes type II; however, evidence from individual 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 mortality with diabetes type II as an underlying cause, although none of the reported results were significant (Karlsson et al. 2005). The evidence for an association between shift work and diabetes type II was reported as limited in a review (X. S. Wang et al. 2011). A review specifically focused on shift work and diabetes upgraded the association to moderate (Knutsson and Kempe 2014), a meta-analysis from 2015 reported that shift work was associated with an increased risk of diabetes type II (Gan et al. 2015).
Cardiovascular disease

CVD is a group of diseases that involves diseases of 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 other causes. CVD related to atherosclerosis are ischemic heart disease (IHD), CHD, and some types of cerebrovascular disease. CVD also consists of diseases in major blood vessels, high blood pressure, peripheral artery diseases (PAD) arrhythmias, and rheumatic heart disease.

Ischemic heart disease and stroke
Atherosclerosis is a complex, often time-consuming, process 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 could result in restrictions in blood flow. These accumulations are prone to rupture, leading to possible formations of blood clots. If a blood clot is developed and lodged in a coronary artery, it can lead to a MI, or if lodged in the brain, an ischemic stroke (Mendis et al. 2011).

IHD, synonymous to CHD, 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 leading to 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 due to an occlusion, in an artery to/or in the brain (WHO 2011).
**Incidence**

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 2013 was 482 cases per 100 000 men and 313 cases per 100 000 women, age 20 and above. This corresponds to just under 28 000 patients (Socialstyrelsen 2014).

The incidence of ischemic stroke in Sweden for men is 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). Recent reports have indicated that stroke incidence is declining in Sweden (Riksstroke 2015). In 2010 in Sweden, the total number of incident cases of ischemic stroke were 20 399, with an incidence rate of 220 cases of ischemic stroke per 100 000 men and 206 per 100 000 women (Socialstyrelsen, 2011a).

**Mortality, case fatality and sudden cardiac death**

CVD related mortality is decreasing in most European countries, but it is still a major cause of death, resulting annually in approximately 1.9 million deaths in the European union, with 1.8 million of those deaths related to CHD (Nichols et al. 2012). The mortality of IHD in Sweden has been declining for some time, during 2014, there were 143 deaths per 100 000 males and 115 deaths per 100 000 women. The same trend has been observed for ischemic stroke as well, the mortality in Sweden in 2015 were 12 deaths per 100 000 males and 18 deaths per 100 000 women (Socialstyrelsen 2015a).

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 and Lundberg 2004). In general, men have a higher case fatality of MI
than women (MacIntyre et al. 2001). There has been a trend towards declining case fatality after MI in Sweden; between the years of 2011 to 2013, only 12.6 % of cases with MI treated in hospital died within 28 days (Socialstyrelsen 2015b).

Sudden cardiac death (SCD) is defined as unexpected and non-traumatic death occurring within one hour of onset of new or worsening symptoms. SCD is often caused by arrhythmias in the heart (Zipes et al. 2006).

Risk factors
Prevention of CVD is based mostly on the identification of individuals at risk, most often by assessing the prevalence of associated risk factors. Numerous risk factors have been implicated in the mechanisms leading up to atherosclerosis related CVD. Traditional risk factors such as age, gender, high blood pressure, dyslipidaemia, smoking, and diabetes form the base of most cardiovascular risk prediction models used for identification of individuals at risk of CVD.

The INTERHEART investigators reported that nine modifiable risk factors associated with incident MI explain more than 90 % of the population attributable risk (PAR) of MI among women and men from all regions of the world (Yusuf et al. 2004). In terms of attributable deaths, the leading CVD risk factor is high blood pressure (to which 13 % of global deaths is attributed), followed by tobacco use (9 %), raised blood glucose (6 %), physical inactivity (6 %) and, overweight and obesity (5 %) (Mendis et al. 2011). Results from INTERSTROKE show that hypertension is the most important risk factor for ischemic stroke. The same study

---

2 Explained in detail later in the text.
3 A global case-control study of risk factors for MI.
4 Current or former tobacco smoking, prevalence of diabetes or hypertension, abdominal obesity, psychosocial stressors, insufficient intake of fruits and vegetables, no alcohol intake, physical inactivity, and elevated blood lipids.
5 A global case-control study of risk factors for stroke.
also reported associations between all of the risk factors used in INTERHEART with ischemic stroke with a similar PAR value (O’Donnell et al. 2010).

**Predicting risk based on risk factors and risk markers**
When referring to something as a risk factor, it is implied that it plays a role in the development of CVD. This is the case for most established CVD risk factors. On the other hand, a risk marker is not assumed to play a direct role in the disease progression, it should be considered as a surrogate for a biological process, or serve as an indicator of subclinical disease. Generally, a risk marker is a poor target for therapy (T. J. Wang 2008) compared to modifiable risk factors.

A risk marker is mainly useful if it improves the ability to predict risk (Pepe et al. 2004; Ware 2006). While predicting risk of CVD is difficult, risk equations like the Framingham risk score has a high capacity of predicting further CVD events (Wilson et al. 1998).

**Modifiable risk factors**
Risk factors for CVD can be divided into modifiable and non-modifiable risk factors. The majority of CVD is caused by risk factors that can be controlled, treated, or modified. For example, high blood pressure, tobacco use, diabetes, physical inactivity, unhealthy diet, elevated cholesterol, and other blood lipids, overweight, and obesity (Anand et al. 2008).

Socioeconomic status (Sahar and Sassone-Corsi 2009; Sephton and Spiegel 2003), is an established risk factor for IHD and ischemic stroke (Peltonen et al. 2000). It is debatable whether socioeconomic status is a modifiable or a non-modifiable risk factor.
Non-modifiable risk factors
In addition to the modifiable risk factors, there are risk factors that cannot be altered or treated in the same way.

Age
CVD becomes increasingly common with advancing age. With advancing age, the heart undergoes physiologic changes, increasing the susceptibility for CVD. For example, the aged heart muscle may relax less completely between beats, resulting in the pumping chambers becoming stiffer and enlarged, thereby may work less efficiently. Such age-related changes may increase the rate of disease development. The negative effects of age on the cardiovascular system need to be separated from effects related to sedentary lifestyle. Some of these age-related changes can be prevented or delayed with increased physical activity (Pugh and Wei 2001).

Family history of cardiovascular disease
A family history of CVD is an independent risk factor for coronary diseases (Weijmans et al. 2015). There are additional ways of defining family history of CVD, for example premature occurrence and, familial aggregation (Pandey et al. 2014). Numerous mechanisms have been discussed in order to explain this further, such as accumulation of both known and unidentified environmental and heritable risk factors (deGoma et al. 2012). It is likely that family history of CVD is a mixture of a number of factors such as early life events (Gluckman et al. 2008) and for example childhood socioeconomic position (van de Mheen et al. 1998) acting together to increase the risk of CVD. Parental history of premature CVD has also been associated with increased accumulation of coronary artery calcium, a risk factor for future CVD in asymptomatic individuals (Pandey et al. 2014).

6 There are different ways of defining premature occurrence; one way is events of CVD occurring before the age of 55 years in male relatives and before 65 years in female relatives (Pandey et al. 2014).
**Gender/sex**
Males are at greater risk of CVD than pre-menopausal females. Once past the menopause, the risk of CVD for females approaches that of males. Risk of stroke however, does not seem to have the same strong age-dependent gender difference. It is generally believed that the fact that women on average have MI later in life is due to the protective effects of female sex hormones, but differences in diet and smoking may also be important in explaining gender differences in CVD (Kannel and Levy 2004; Lawlor et al. 2001).

In reporting risk factor distribution among controls in the INTERHEART study, it is possible to get a picture of gender differences. The distribution of risk factors varied significantly between males and females. Fewer women than men had elevated blood lipids, were current or former smokers, performed regular physical activity, and fewer women were alcohol consumers. Moreover, women were significantly more likely to have high blood pressure compared to men (Anand et al. 2008).

Risk factors, which were more strongly associated with MI in women compared to men, included high blood pressure, diabetes, alcohol intake, and physical activity. Only former smoking was more strongly associated with MI in men compared to that in women. The association of current smoking, unhealthy diet, abdominal obesity, and psychosocial risk factors for MI did not vary significantly by sex. Generally, risk factors were more strongly associated with MI in younger (60 years) compared to older (above 60 years) women and men. Interestingly, the protective effects of physical activity and MI and regular alcohol consumption and MI were stronger among older men than younger men (Anand et al. 2008).

Largely speaking, similar risk factor associations with MI are present in women and men for elevated blood lipid levels, current smoking, abdominal obesity,
unhealthy diet, and psychosocial stress factors. There are studies showing sex/gender differences, influenced by age, in blood lipids and BMI and WHR. For older women, a slightly higher BMI is likely to be associated with lower all-cause mortality whereas central obesity measured via WHR is associated with an increased mortality. These findings were not found in younger women (Lindqvist et al. 2006). There are also age-specific associations showing that high cholesterol is more important for younger women and high triglycerides are more important for older women regarding both mortality and incidence of MI (Lindquist et al. 2002). The gender/sex risk differences in CVD in associations to blood lipids have been known for some time (Lapidus et al. 1985; Wilhelmsen et al. 1973). Risk factors for CVD have been reported to be associated with a higher relative risk of MI for women compared to men (Reuterwall et al. 1999). On average, women experience their first MI nine years later than men do. This is probably related to higher risk factor prevalence among men at earlier age (Anand et al. 2008), but also to hormonal differences (Kannel and Levy 2004; Lawlor et al. 2001).

**Interaction between risk factors**

Interaction\(^7\) refers to when the effects of two factors present at the same time are greater than the effects of each individual factor. A number of studies have studied interaction between multiple risk factor exposure and CVD outcome.

For example, in 1999, Reuterwall and co-workers analysed the interaction between gender and the different risk factors was evaluated from the estimated crude relative risk (RR), using departure from additivity as the measurement of interaction. Synergy index (SI), was calculated. They analysed a number of risk factors (diabetes, total cholesterol, triglycerides, high blood pressure, overweight, abdominal obesity, physical inactivity, smoking, adjusted for previous smoking and job strain) in order to understand if they interacted with gender on the risk of

\(^7\) Interaction is explained further in the methods section.
MI (Reuterwall et al. 1999). They showed that SI ranged from 1.04 for high blood pressure, 1.41 and 1.49 for total cholesterol and triglycerides, 1.18 for diabetes, 1.2 for overweight, 1.56 of abdominal obesity, 1.28 for physical inactivity, 1.1 for job strain to the strongest interaction at an SI of 1.79 for smoking (Reuterwall et al. 1999).

**Other types cardiovascular disease**
The following paragraphs are an overview of other major types of CVD. The four main types of arrhythmia are premature (extra) beats, supraventricular arrhythmias, ventricular arrhythmias, and bradyarrhythmias. Premature heartbeats is the most common type of arrhythmia and can have both atrial and ventricular origin. Supraventricular arrhythmias are tachycardia that starts in the atria or atroventricular (AV) node.

*Atrial fibrillation and atrial flutter*
Atrial fibrillation (AF) is the most common type of serious arrhythmia. It involves a very fast and irregular contraction of the atria. As a result, the atrium is not able to pump blood into the ventricles as needed. The risk of AF increases with age, stroke and heart failure are the two major complications of AF (Camm et al. 2010). In atrial flutter, the heartbeat is fast and regular and it is much less common than AF, but has similar symptoms and complications (Blomstrom-Lundqvist et al. 2003).

**Heart failure**
Heart failure can be defined as when the heart is unable to pump out enough oxygenated blood to the body. As the heart is pumping less effectively, blood may back up in other areas of the body, resulting in, for example ankle swelling. The most common causes of heart failure are coronary artery disease, high blood pressure and diabetes (McMurray et al. 2012).
**Rheumatic heart disease**

Rheumatic heart disease is caused by damage to the heart valves and heart muscle from inflammation and scarring caused by rheumatic fever. Rheumatic fever is caused by an abnormal bodily response to a streptococcal bacterial infection, usually beginning as sore throat or tonsillitis in children. The incidence of rheumatic fever is declining most parts of the world and is lower in developed countries (Seckeler and Hoke 2011).

**Artery disease**

Artery disease can be related to the progression of atherosclerosis but can also be caused by for example trauma, radiation injury, aneurysms⁸, and diseases that cause vascular inflammation. There are a number of different types of artery diseases, for example PAD, describe a restricted circulation in at least one peripheral artery. Other examples are artery disease of the kidney, or the brain (Hiatt et al. 2008).

**Shift work and morbidity of coronary heart disease**

A growing body of evidence have studied the association between shift work and CHD, the major part with positive findings with a number of studies exemplified from here on.

Alfredsson and co-workers (1982) did not find any association between shift work and MI in a case-control study of 1 216 participants. The exact prevalence of shift work was not stated, (RR 1.25 (95 % confidence interval (CI) 0.97–1.62)) (Alfredsson et al. 1982). Falger and Schouten (1992) did a case-control study analysing the association between MI and workers with prolonged or irregular working hours or shift work. They did not find any association (OR 1.16 (95 % CI 0.68-2) for the 458

---

⁸ Malformation of a blood vessel.
participants (99 cases with exposure to the specified working schedule) (Falger and Schouten 1992).

Alfredsson and co-workers (1985) followed 958 069 participants in a cohort study analysing hospitalisation for MI. They reported that the standardised mortality ratio\(^9\) for exposure to irregular working hours was 115 (95 % CI 104-126) for men and, 152 (95 % CI 119-191) for women. The exact number of participants with irregular working hours was not stated (Alfredsson et al. 1985). Knutsson and co-workers (1986) used a prospective cohort design, where 504 (78 % shift workers) participants were followed using IHD as the main outcome variable. The study reported that shift work was associated with IHD after 11 to 20 years exposure (RR 2.2 for 11-15 years of shift work and RR 2.8 for 16-20 years of shift work) (Knutsson et al. 1986). Kawachi and co-workers (1995) did a prospective cohort study that comprised 79 109 (40.6 % shift workers) female nurses, they reported a RR of CHD of 1.38 (95 % CI, 1.08-1.76) (Kawachi et al. 1995). In 1999, Knutsson and co-workers (1999) did a case-control study comprising 4 648 participants with 252 male cases of MI exposed to shift work; the corresponding number for females was 97. The study analysed 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 1.1-1.6) for men and 1.3 (95 % CI 0.9-1.8 for women) (Knutsson et al. 1999).

Haupt and co-workers (2008) used data from a cross-sectional survey to analyse if shift work was associated with atherosclerosis and MI, among 2 510 participants (28 % shift workers). They found that shift work was associated with atherosclerosis and that the hazard ratio (HR) for younger shift workers risk of MI was 1.53 (95 % CI 1.06–2.22) (Haupt et al. 2008).

\(^9\) A way of quantifying an increase or decrease in mortality in a study compared to the general population.
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 and 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 assessment of the results in the included studies (Frost et al. 2009). A later review concluded that there was moderate support for the association between shift work and CVD. In comparison to some of the other reviews on this issue, this was somewhat more transparent in its grading of their findings by the use of Royal College of General Practitioners three-star system (X. S. Wang et al. 2011) in assessment of the included publications.

A meta-analysis from 2012 that comprised 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 (risk ratio 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). That study had rather generous inclusion criteria, resulting in an analysis conducted on an extensive body of evidence. They included older studies that usually do not appear in the discussion on the association between shift work and CVD (Vyas et al. 2012). The issue of study quality in early studies on shift work and CVD has been addressed previously (Kristensen 1989). In their generous inclusion criteria, there is a risk of bias regarding 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 shift work exposure.

**Shift work and cardiovascular disease mortality**

A number of studies have analysed if CVD mortality is greater for shift workers compared to day workers. Rafnsson and Gunnarsdottir (1990) found, in their retrospective cohort study of 160 shift workers, that the standardized mortality ratio for IHD mortality was 125 for (Rafnsson and Gunnarsdóttir 1990). Another cohort study reported a standardised relative rate for CHD related mortality of 1.24 (95 % CI 1.04-1.49) among shift workers with at least 30 years of shift work exposure. In that study, 43 % of the 5 442 participants were shift workers (Karlsson et al. 2005). Fujino and co-workers (2006) followed 17 649 male industrial workers (11.5 % shift workers and 4.9 % night workers) in a prospective cohort study. They found that shift workers was associated with an increased risk of IHD mortality compared to day workers (RR 2.32, 95 % CI 1.37-3.95). Permanent night work on the other hand, was not associated with increased risk of IHD (RR 1.23 95 % CI 0.49 - 3.10 (Fujino et al. 2006).

A number of other studies did not find any support for the association between shift work and CVD mortality, reporting risk estimates ranging from 0.64 to 1.22. McNamee and co-workers (1995) reported an OR of 0.90 (90 % CI 0.68–1.21) in a case-control study among their 934 participants (305 cases of IHD exposed to shift work) for coronary mortality (McNamee et al. 1996). In a nested case-control study, Steenland and Fine (1996) reported that shift work was not associated with an increased IHD mortality (OR of 0.64 (95 % CI 0.28–1.47)) in 21 491 study participants (163 mortal cases of IHD exposed to shift work) (Steenland and Fine 1996). Bøggild and co-workers (1999) reported, in a prospective cohort study comprising 5 249 participants (208 cases of IHD exposed to shift work), no association between shift work and IHD (OR 0.9 (95 % CI 0.7-1.1)) (Bøggild et al.
A retrospective cohort study comprising over 138,000 person-years (exact shift work prevalence not reported) reported no increased CVD mortality related to shift work. But shift work was associated with increased cerebrovascular mortality (rate ratio 1.19 (95 % CI 1.01-1.39)) but not night work (rate ratio 1.06 (95 % CI 0.86-1.31)) (Virtanen and Notkola 2002).

A cohort study from Germany on male industrial workers reported that shift work was not associated with increased IHD-related mortality (HR 0.77 (95 % CI 0.52-1.14)). The study comprised 31,143 participants, 45 % shift workers (Yong et al. 2014). In a cohort study from 2010, Hublin and co-workers followed 20,142 participants (9.5 % shift workers and 1.7 % night workers) analysing if shift work was associated with CHD mortality. The HR 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 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 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 2011). All this may result in physicians having insufficient information about the patient, contributing to the issues regarding mortality studies based on death certificates.

**Shift work and risk factor interaction**

Interaction describes a situation where the exposure to multiple risk factors, in this case to CVD such as smoking or elevated blood pressure and shift work, results in a greater risk increase for MI compared to the single risk factor exposure.
Tenkanen and co-workers (1998) have previously studied the joint effect of risk factor and shift work exposure and its association with CHD. They also studied the effects of multiple exposures of the included risk factors and their association with CHD. They concluded that there was a joint effect of shift work with the included risk factors (smoking, low leisure physical activity, and BMI ≥28) which increased the risk of CHD from 87 % to 169 % (Tenkanen et al. 1998). Another study found that exposure to any two or three of shift work, noise, and physical workload increased the RR of CHD with around 30 % to 70 %. They proposed that noise exposure could affect both short- and long-term processes related to atherosclerosis (Virkkunen et al. 2006). There is a joint effect of shift work and high blood pressure on the risk of CHD (Virkkunen et al. 2007).

However, analysing the joint effects is only performing a part of an interaction analysis. Knutsson and co-workers (1999) studied interaction as departure from additivity\textsuperscript{10} using SI among shift workers. They found no interaction between shift work and job strain on the risk of MI (SI 0.7 (95 % CI 0.3 to 1.4)) (Knutsson et al. 1999).

**Shift work and parental history of cardiometabolic disease**

Pietroiusti and co-workers (2010) adjusted their results for family history of cardiometabolic disease or comorbidity\textsuperscript{11} when studying the association between shift work and the metabolic syndrome. They found no increased association related to family history of metabolic syndrome and the risk of metabolic syndrome. Kawamaki and co-workers (1999) showed that a family history of diabetes was associated with an increased risk of diabetes type II (HR 2.45 (95 % CI

\textsuperscript{10} Explained in detail in the methods section.

\textsuperscript{11} Defined as a family history of either obesity, high blood pressure, elevated blood lipids, diabetes, IHD, or a combination of the listed diagnoses or risk factors.
1.09-5.53). No other studies that investigated the association or interaction between shift work and family history of CVD were found.

**Shift work and ischemic stroke**

A few studies have analysed the association between shift work and incidence of ischemic stroke, or the association with ischemic stroke mortality.

A retrospective cohort study of 5442 participants, 43% shift workers reported that shift work was not associated with increased mortality from ischemic stroke (standardised relative rate 1.56 (95% CI 0.98-2.51)) (Karlsson et al. 2005). One study did not find any association between the incidence of ischemic stroke and shift work (odds ratio (OR) of 1.0 (95% CI 0.6-1.8)). That was a case-control study of 607 participants that included 44 cases of ischemic stroke that were exposed to shift work (Hermansson et al. 2007). Another study found an association between ischemic stroke and shift work for female nurses working rotating shift with night shifts. The study was based on a prospective cohort comprising 80108 participants, 59.5% had at some point been engaged in one or more years of shift work. They reported a HR of 1.04 (95% CI 1.01–1.07), for 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 meta-analysis resulting in a risk ratio of 1.05 (95% CI 1.01-1.09) (Vyas et al. 2012). In a systematic review published in 2013, the authors concluded that the epidemiological evidence for an association between shift work and ischemic stroke was limited (Jakobsson and Gustavsson 2013).
Potential mechanisms affecting cardiovascular disease and 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
Circadian disruption and stress related to interference with the metabolic and hormonal functions are examples of proposed pathways linking shift work to CVD and other chronic conditions (Green et al. 2008). Melatonin has been proposed to play a vital role in preventing oxidative stress, and may hold part in the explanation behind the risks associated with circadian disruption (Faraut et al. 2013). A study from 2015 indicated that lack of sleep can lead to acute epigenetic changes and altering of metabolically important tissues clock genes (Cedernaes et al. 2015). This is another mechanism that could hold part of the explanation behind the association between shift work and metabolic disorders such as type II diabetes.

Metabolic disturbance
Shift work has been associated with obesity, metabolic syndrome, diabetes and dyslipidaemias (Ulhoa et al. 2015). 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). Unhealthy dietary patterns (Wirth et al. 2014) are also likely to play a part in the association between metabolic disturbances and shift work.
Life style factors and stress
Shift work has been also been associated with circadian disruption that could affect behaviour like sleep–wake patterns, sleep debt, insomnia, and sleepiness. Shift work has also been associated with tobacco smoking, alcohol consumption and, unhealthy dietary patterns (Puttonen et al. 2010). 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 (Wirth et al. 2014; Zhao and Turner 2008). The misalignment between social and biological time, sometimes referred to as social jetlag, affects shift workers to some extent. It has been associated with unhealthy behaviours (Wittmann et al. 2006), and was put forward as one of the most important issues in explaining the association between shift work and disease (Bøggild and Knutsson 1999).

Cardiovascular effects
Shift work is associated with subclinical atherosclerosis (Haupt et al. 2008) and markers of systemic inflammation (Puttonen et al. 2010; Puttonen et al. 2011). In a study in Finnish middle-aged men, weekend shift work appeared to accelerate the formation of carotid atherosclerosis, at an even greater speed among men with pre-existing CVD (A. Wang et al. 2015). It is possible that the arteries of shift workers are more affected by atherosclerosis, this would could be related to a weakened inside (intima) of the blood vessel and thereby increasing the risk of atherosclerosis that later could rupture and cause a thrombosis. It would also be of interest to study the potential association between shift work and markers of vascular inflammation, such as Apo-lipoprotein-associated phospholipase A2 (Lp-PLA2) (Rudolf and Lewandrowski 2014). Such studies could bring further understanding to the potential pro-inflammatory effects of shift work.

Shift work has also been associated with arrhythmias (Härenstam et al. 1987; van Amelsvoort et al. 2001), prolonged QTc interval, and conduction disorders (Meloni
et al. 2013), which in term may indicate a poorer prognosis after a MI, and at the same time imply that shift work may affect the functionality of the heart muscle. Low heart rate variability (HRV) is an established method for assessing cardiac autonomic regulation (Malik et al. 1996), and has been associated with greater risk of CVD in a meta-analysis from 2013 (Hillebrand et al. 2013). Low HRV was reported to be associated with night shift work in a study from South Korea (S. Lee et al. 2015). In a study from 2015, the authors reported an association between lifetime exposure to shift work and unfavourable changes in autonomic cardiac control related to a decrease in parasympathetic modulation, indicating a higher level of cardiac stress. The same study also reported an association between lifetime exposure to shift work and increased blood pressure (Souza et al. 2015). There are other studies that also support an association between shift work and high blood pressure, for example (Ohlander et al. 2015), while other studies do not (Gholami-Fesharaki et al. 2014; Gholami Fesharaki et al. 2014). Shift work is likely to have negative cardiac effects, but more research is needed to further explain this area.

**Summary**

There are evidence supporting the association between shift work and increased risks of CVD. There may be a number of mechanisms involved in these associations, such as sleep disturbance, cardiac effects, and associated sedentary lifestyle factors. More research is needed to establish the contribution of these mechanisms to the association between shift work and CVD.
AIM AND OBJECTIVES

The aim of this thesis was to further study the association between shift work and CVD 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?
- Does shift work interact with CVD risk factors to increase the risk of MI?
- Does shift work interact with parental history of MI or SCD to increase the risk of MI?
METHODS

Study populations

The following chapter gives a description of the study populations and analytical approaches utilised in papers I-IV.

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). The 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 finding was 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 (B Stegmayr and 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-9 434) and no signs of hemorrhage in a computed tomography (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 (B. Stegmayr et al. 1994). For each case, five matched controls without known CVD and cancer were selected from the MONICA and VIP cohorts.
**SHEEP/VHEEP (paper II, III, and IV)**
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.

Case fatality in paper II was the proportion of cases with first time MI consistent with the previously described criteria, which were fatal within 28 days after the event.

Paper III and paper IV used the following definition of MI cases. 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 was 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 fatal cases, questionnaire information was obtained from a close relative three to six months after the occurrence of MI. To reduce the risk of including participants that were retired, the age limit for inclusion in the analyses was set to 65 years and unemployed or retired cases were excluded.

**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, high blood pressure, and job strain were assessed through questionnaire data, and sometimes completed with data from health examinations as the case for BMI.

In paper I, the shift work variable was based on the responses to two questions from the population surveys, since the question regarding work hours was not consistent in all the surveys. One question was from the VIP study [“Do you have shift work or weekend work? yes (a) or no (b)”], and the other question came from the MONICA study [“What are your normal work hours? Regular work hours (a), shift work (b), variable work hours (c) and I am not gainfully employed (d)”]. The respondents who answered “a” to the first question and those who responded “b” or “c” to the second question were regarded as shift workers.

In paper II-IV, shift work exposure was assessed through the following questions: (1) Did you undertake shift work (during the most recent 5 years of work)? If the answer was yes, the respondent was asked to add information about the type of shift schedule. (2) To reduce the risk of including participants that were retired, the age limit for inclusion was set to 65 years, and unemployed or retired cases were excluded. The second question concerned when during the day that the majority of
the work hours was scheduled. The response alternatives were (a) 06:00–18:00, (b) 18:00–22:00, (c) 22:00–06:00, (d) a combination of (a) and (b), (e) a combination of (b) and (c), (f) a combination of (a) and (c), and (g) a combination of (a), (b), and (c). If a participant answered yes to question one or chose response alternatives b–f to question two, he or she was regarded as being exposed to shift work (14.2 %). If the respondent answered no to question 1 and did not chose alternatives b–f of question 2, the respondent was regarded as day worker (85.7 %), and only 0.2 % of the respondents were excluded because their answers were not possible to categorise.

Low level of leisure time physical activity was considered when a respondent indicated that he or she did a minimum of physical activity in their leisure time; this was compared to respondents that were engaged in moderate physical activity up to training and competing in different sports. Current tobacco smoking was compared to non-smokers. Respondents that reported that they had quit smoking more than one year ago were considered as non-smokers in paper I. In paper II, current smokers included respondents who had stopped smoking within the last 2 years before inclusion, and non-smokers included respondents quitting more than 2 years ago. Occasional smokers were excluded from the analyses; thereby some relevant cases of current smokers were lost. However, given the variance inherited in that variable, it is likely that this contributes to a higher validity in the results.

BMI was analysed at BMI ≥ 28 as an indicator of sub-clinical obesity (Thomas et al. 2001), usually defined as BMI ≥ 30.

Diabetes type II was considered at a level of fasting glucose above 6.7 mmol/L or self-reported diabetes type II in the questionnaire, or if a respondent required insulin or regularly medicated for disease consistent with ICD 9-code 250, or if reported pharmacological treatment against diabetes type II in the questionnaire.
Educational level was used as a proxy variable to estimate socio-economic status. Cases with compulsory school (9 years) as their highest education were considered to have low socio-economic status; participants with education longer than 9 years were used as reference.

The concept of job strain was introduced in 1979 (Karasek 1979). Job strain was measured using a short version of the questionnaire in Swedish (Theorell et al. 1988). It had five questions about psychological demands and six questions about decision latitude, each with four graded responses ranging from 1=never to 4=always or almost always. The work experience during the last 5 years prior to inclusion in the study was considered. The variable was based on the individual quota between demand and control. Job strain was considered present for the respondents who were in the upper tertile for the demand questions and the lower tertile for decision latitude.

Blood lipids were based on fasting samples, participants with total serum triglyceride levels of ≥ 2.3 mmol/l or total serum cholesterol levels of ≥ 6.45 mmol/l were considered at risk. Data on blood lipids were not available for deceased cases of MI in paper II.

In paper I, high blood pressure was identified if a participant had a systolic pressure of ≥ 140 mmHg and/or a diastolic pressure of ≥90 mmHg or was on antihypertensive medication. In paper II and III, high blood pressure was considered present at either ≥ 170 mmHg in systolic or ≥ 95 mmHg in diastolic blood pressure, or pharmacological treatment for disease consistent with ICD 9-code 40, or earlier pharmacological treatment for high blood pressure that ended less than 5 years before inclusion in the study.
**Statistical methods**

All calculations were, when so was possible, 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 or less was considered significant in the chi-square tests or independent samples t-test. In all papers, associations between shift workers outcome variables were assessed using logistic regressions. In logistic regressions analyses and the interaction analyses, the 95 % CI could not contain 1 in order to be considered significant.

**Interaction on an additive scale**

Additive interaction between two risk factors for risk of an outcome is described as:

$$A_1B_1 - A_0B_1 - A_1B_0 + A_0B_0$$

For two dichotomous factors A and B: $A_1B_1$ is when both factors A and B are present, $A_1B_0$ is when factor A is present but factor B is absent, $A_0B_1$ is when if factor A is absent but factor B is present. $A_0B_0$ is the reference category where none of the exposures is present.

In paper III and paper IV, interaction as departure from additivity was using the following approach. Logistic regression analyses were performed on shift work and CVD risk factors, where the risk factors were included as categorical indicator variables (with $A_0B_0$ as reference). The results of these calculations were performed in order to derive the OR $A_1B_1$, OR $A_1B_0$, and OR $A_0B_1$ as components for the included interaction analyses.

Interaction between shift work and the parental MI or SCD was analysed by using RR due to interaction (RERI), attributable proportion due to interaction (AP) and
Rothmans SI with 95% CI (Kalilani and Atashili 2006; Rothman et al. 2008). RERI, AP and SI and 95% CI were calculated using a previously published and publicly accessible SAS program (Lundberg et al. 1996).

\[ RERI = \frac{OR_{A_1B_1} - OR_{A_1B_0} - OR_{A_0B_1} + 1}{OR_{A_1B_1}} \]

RERI = 0 means no interaction or exactly additivity; RERI > 0 means positive interaction or more than additivity; RERI < 0 means negative interaction or less than additivity; RERI can go from - infinity to + infinity. RERI was considered significant when the 95% CI did not contain 0.

\[ AP = \frac{RERI}{OR_{A_1B_1}} \]

AP = 0 means no interaction or exactly additivity; AP > 0 means positive interaction or more than additivity; AP < 0 means negative interaction or less than additivity; AP can go from –1 to +1. AP was considered significant when the 95% CI did not contain 0.

\[ SI = \frac{OR_{A_1B_1} - 1}{(OR_{A_1B_0} - 1) + (OR_{A_0B_1} - 1)} \]

SI = 1 means no interaction (the sum of effects due to multiple causes). SI > 1 refers to a positive interaction and SI < 1 refers to a negative interaction. SI was considered significant when the 95% CI did not contain 1.

All of the statistical calculations were carried out using the statistical software SPSS 12.0 for paper I, SPSS 16.0 for paper II, paper III 17.0, and paper IV 21.0 (SPSS Inc. Chicago, IL, USA). Measures of interaction were calculated in SAS 9.1 for Windows.
Ethical considerations

Both studies (MONICA and SHEEP/VHEEP) conformed to the principles of the Helsinki Declaration of 1964, and were approved by Regional Ethical Committees in Sweden. When reporting potential risks associated with an individual’s occupation, there is a risk that this will affect the individuals negatively. For example, they can feel less motivated towards their work. On the other hand, not reporting such risk associations would keep the same individuals uninformed of the potential risk exposure. Conducting research on shift work increases the opportunity for prevention and early detection of CVD. By that, the benefits for the shift workers are likely to supersede the negative effects of the information from this type of research.
RESULTS

Shift work and ischemic stroke (paper I)

The analyses in paper I included 194 cases of ischemic stroke, of which 44 cases were exposed to shift work. No differences were found between the day workers and shift workers regarding the prevalence of the assessed risk factors.

Table 1: Age-adjusted odds ratios (OR) and 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 analyses.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95 % CI</td>
<td>OR 95 % CI</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shift work</td>
<td>1.0 0.6-1.8</td>
<td>1.0 0.6-1.8</td>
</tr>
<tr>
<td>Shift work, adjusted for job strain</td>
<td>1.3 0.7-2.3</td>
<td>1.0 0.5-1.9</td>
</tr>
<tr>
<td>Shift work, adjusted for smoking</td>
<td>1.0 0.6-1.8</td>
<td>1.1 0.6-2.0</td>
</tr>
<tr>
<td>Shift work, adjusted for low educational level</td>
<td>1.0 0.6-1.9</td>
<td>1.1 0.6-2.0</td>
</tr>
<tr>
<td>Shift work, adjusted for job strain, smoking, low educational level</td>
<td>1.2 0.6-2.3</td>
<td>1.0 0.6-2.0</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shift work, adjusted for high triglycerides</td>
<td>1.0 0.5-2.0</td>
<td>1.0 0.5-1.9</td>
</tr>
<tr>
<td>Shift work, adjusted for high total cholesterol</td>
<td>1.0 0.5-1.8</td>
<td>0.9 0.5-1.6</td>
</tr>
<tr>
<td>Shift work, adjusted for high blood pressure</td>
<td>0.9 0.5-1.8</td>
<td>0.6 0.3-1.2</td>
</tr>
<tr>
<td>Shift work, adjusted for high triglycerides, high total cholesterol, high blood pressure</td>
<td>1.1 0.5-2.2</td>
<td>0.9 0.4-1.7</td>
</tr>
</tbody>
</table>

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.
Shift work and case fatality of myocardial infarction (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. There were marked differences between day- and shift workers regarding current tobacco smoking, BMI above 28 and low socioeconomic status for both men and women. Physical inactivity, job strain and 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).

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

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95 % CI</td>
</tr>
<tr>
<td>Shift work</td>
<td>1.6</td>
<td>1.1-2.4</td>
</tr>
<tr>
<td>Shift work, adjusted for physical inactivity</td>
<td>1.6</td>
<td>1.1-2.3</td>
</tr>
<tr>
<td>Shift work, adjusted for current tobacco smoking</td>
<td>1.7</td>
<td>1.1-2.4</td>
</tr>
<tr>
<td>Shift work, adjusted for BMI ≥ 28</td>
<td>1.6</td>
<td>1.1-2.4</td>
</tr>
<tr>
<td>Shift work, adjusted for diabetes type II</td>
<td>1.7</td>
<td>1.1-2.4</td>
</tr>
<tr>
<td>Shift work, adjusted for low socioeconomic status</td>
<td>1.4</td>
<td>0.8-2.3</td>
</tr>
<tr>
<td>Shift work, adjusted for high blood pressure</td>
<td>1.8</td>
<td>1.2-2.7</td>
</tr>
<tr>
<td>Shift work, adjusted for job strain</td>
<td>1.6</td>
<td>1.1-2.4</td>
</tr>
<tr>
<td>Shift work, adjusted for BMI ≥ 28, diabetes type II and high blood pressure</td>
<td>2.2</td>
<td>1.5-3.2</td>
</tr>
<tr>
<td>Shift work, adjusted for physical inactivity, current tobacco smoking, low socioeconomic status and job strain</td>
<td>1.7</td>
<td>1.1-2.6</td>
</tr>
</tbody>
</table>
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 high blood pressure in a multivariate regression model in order to analyse the associations related to medical risk factors, the OR for male shift workers was 2.2. In the multivariate regression model with risk factors 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 performed. 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).

**Shift work, risk factor interaction and myocardial infarction (paper III)**

The analyses in paper III was conducted on 4 648 participants, including 1 417 (44 %) male and 589 (41 %) female cases of MI. Shift work was more common among cases with MI in both men 17.8 % vs. 12.4 % (p <0.001), and women 16.5 % vs. 10.2 % (p <0.001).
Table 3 show SI as a measure of interaction between shift work and the specific risk factor. The results showed an interaction between physical inactivity and shift work on the risk of MI for males. For females, interactions were found between shift work and high WHR or elevated triglycerides.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  (95 % CI)</td>
<td>SI (95 % CI)</td>
<td>OR  (95 % CI)</td>
<td>SI (95 % CI)</td>
</tr>
<tr>
<td><strong>BMI ≥ 28 (n=4 593)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 28 and dw</td>
<td>1.67 (1.41-1.99)</td>
<td>1.52 (1.18-1.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 28 and sw</td>
<td>1.77 (1.39-2.25)</td>
<td>1.70 (1.14-2.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 28 and sw</td>
<td>1.65 (1.19-2.29)</td>
<td>0.45 (0.19-1.07)</td>
<td>2.31 (1.38-3.84)</td>
<td>0.7 (0.37-3.08)</td>
</tr>
<tr>
<td><strong>Current smoker (CM) (n=4 648)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CM and dw</td>
<td>2.33 (1.99-2.74)</td>
<td>3.36 (2.62-4.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker and sw</td>
<td>1.48 (1.12-1.94)</td>
<td>1.33 (0.84-2.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM and sw</td>
<td>3.06 (2.31-4.06)</td>
<td>1.14 (0.71-1.83)</td>
<td>5.73 (3.57-9.19)</td>
<td>1.76 (0.94-3.31)</td>
</tr>
<tr>
<td><strong>WHR a (n=3 311)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>WHR and dw</td>
<td>1.75 (1.41-2.17)</td>
<td>1.41 (1.04-1.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-WHR and sw</td>
<td>1.38 (1.05-1.81)</td>
<td>1.38 (0.86-2.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHR and sw</td>
<td>1.47 (0.97-2.24)</td>
<td>0.42 (0.11-1.61)</td>
<td>4.17 (2.19-7.92)</td>
<td>4.0 (1.12-14.28)</td>
</tr>
<tr>
<td><strong>Physically inactivity (PI) (n=4 614)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PI and dw</td>
<td>1.52 (1.30-1.78)</td>
<td>2.33 (1.84-2.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non PI and sw</td>
<td>1.33 (1.03-1.73)</td>
<td>1.84 (1.18-2.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI and sw</td>
<td>2.74 (2.03-3.71)</td>
<td>2.05 (1.07-3.92)</td>
<td>3.85 (2.42-6.14)</td>
<td>1.32 (0.65-2.67)</td>
</tr>
<tr>
<td><strong>Elevated triglycerides (ET) b (n=3 076)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ET and dw</td>
<td>2.32 (1.85-2.90)</td>
<td>2.46 (1.7-3.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non ET and sw</td>
<td>1.38 (1.04-1.83)</td>
<td>1.37 (0.88-2.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET and sw</td>
<td>3.22 (1.97-5.25)</td>
<td>1.32 (0.6-2.9)</td>
<td>9.40 (3.85-22.92)</td>
<td>5.69 (1.67-19.38)</td>
</tr>
<tr>
<td><strong>Elevated cholesterol (EC) c (n=3 284)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>EC and dw</td>
<td>1.56 (1.3-1.88)</td>
<td>2.14 (1.61-2.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non EC and sw</td>
<td>1.30 (1.0-1.74)</td>
<td>1.97 (1.19-3.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC and sw</td>
<td>2.21 (1.51-3.25)</td>
<td>1.34 (0.6-3.0)</td>
<td>3.72 (2.12-6.53)</td>
<td>1.68 (0.6-5.13)</td>
</tr>
</tbody>
</table>
Table 4 shows that there was an association and interactions between paternal history of MI or SCD and shift work on the MI risk for male shift workers. The SI was 2.39 and the AP result indicates that around 40% of MI occurring in male shift workers with parental history of MI or SCD were attributed to an interaction between two components. Interaction between shift work and parental MI or SCD, adding both parental and maternal cases together was also analysed, without finding any interactions (results not reported). No other results were found.
Table 4. OR for each of the exposure scenarios and interaction expressed as RERI, AP, and SI with 95% CI, between shift work and analysed risk factors for males. Number of included participants in each analysis, all estimates were adjusted for age

<table>
<thead>
<tr>
<th></th>
<th>N cases</th>
<th>N controls</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father MI or SCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1136</td>
<td>1509</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Father MI or SCD</td>
<td>143</td>
<td>157</td>
<td>1.45</td>
<td>(1.20-1.76)</td>
</tr>
<tr>
<td>Shift work</td>
<td>257</td>
<td>245</td>
<td>1.20</td>
<td>(0.94-1.53)</td>
</tr>
<tr>
<td>Father MI or SCD &amp; shift work</td>
<td>50</td>
<td>23</td>
<td>2.88</td>
<td>(1.75-4.57)</td>
</tr>
<tr>
<td>Measures of interaction on additive scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RERI</td>
<td></td>
<td></td>
<td>1.32</td>
<td>(-0.35-2.29)</td>
</tr>
<tr>
<td>AP</td>
<td></td>
<td></td>
<td>0.40</td>
<td>(0.08-0.73)</td>
</tr>
<tr>
<td>SI</td>
<td></td>
<td></td>
<td>2.39</td>
<td>(1.02-5.60)</td>
</tr>
<tr>
<td>Father MI before 65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1164</td>
<td>1518</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Father MI before 65 years</td>
<td>99</td>
<td>85</td>
<td>1.55</td>
<td>(1.14-2.09)</td>
</tr>
<tr>
<td>Shift work</td>
<td>171</td>
<td>166</td>
<td>1.39</td>
<td>(1.10-1.74)</td>
</tr>
<tr>
<td>Father MI before 65 years &amp; shift work</td>
<td>22</td>
<td>14</td>
<td>2.04</td>
<td>(1.04-4.00)</td>
</tr>
<tr>
<td>Measures of interaction on additive scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RERI</td>
<td></td>
<td></td>
<td>0.12</td>
<td>(-1.48-1.71)</td>
</tr>
<tr>
<td>AP</td>
<td></td>
<td></td>
<td>0.05</td>
<td>(-0.63-0.74)</td>
</tr>
<tr>
<td>SI</td>
<td></td>
<td></td>
<td>1.10</td>
<td>(0.29-4.15)</td>
</tr>
<tr>
<td>Mother MI or SCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1161</td>
<td>1507</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mother MI or SCD</td>
<td>146</td>
<td>115</td>
<td>1.74</td>
<td>(1.34-2.24)</td>
</tr>
<tr>
<td>Shift work</td>
<td>168</td>
<td>155</td>
<td>1.46</td>
<td>(1.16-1.85)</td>
</tr>
<tr>
<td>Mother MI or SCD &amp; shift work</td>
<td>25</td>
<td>25</td>
<td>1.31</td>
<td>(0.75-2.29)</td>
</tr>
<tr>
<td>Measures of interaction on additive scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RERI</td>
<td></td>
<td></td>
<td>-0.97</td>
<td>(-1.9-0.04)</td>
</tr>
<tr>
<td>AP</td>
<td></td>
<td></td>
<td>-0.66</td>
<td>(-1.66-0.34)</td>
</tr>
<tr>
<td>SI</td>
<td></td>
<td></td>
<td>0.33</td>
<td>(0.06-1.94)</td>
</tr>
<tr>
<td>Mother MI before 65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1172</td>
<td>1525</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mother MI before 65 years</td>
<td>34</td>
<td>28</td>
<td>1.58</td>
<td>(0.95-2.62)</td>
</tr>
<tr>
<td>Shift work</td>
<td>179</td>
<td>173</td>
<td>1.40</td>
<td>(1.12-1.75)</td>
</tr>
<tr>
<td>Mother MI before 65 years &amp; shift work</td>
<td>14</td>
<td>7</td>
<td>2.59</td>
<td>(1.04-6.43)</td>
</tr>
<tr>
<td>Measures of interaction on additive scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RERI</td>
<td></td>
<td></td>
<td>0.65</td>
<td>(-1.99-3.30)</td>
</tr>
<tr>
<td>AP</td>
<td></td>
<td></td>
<td>0.24</td>
<td>(-0.53-1.00)</td>
</tr>
<tr>
<td>SI</td>
<td></td>
<td></td>
<td>1.59</td>
<td>(0.31-8.24)</td>
</tr>
</tbody>
</table>

AP attributable proportion due to interaction, MI myocardial infarction, OR odds ratio, RERI relative excess risk due to interaction, SCD sudden cardiac death, SI synergy index, 95% CI 95% confidence interval
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. Moreover; the results show interaction between some CVD risk factors and shift work and finally, parental history of MI or SCD interacts with shift work for males but not for females.

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 another 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 analysis regarding the effects of shift work but claimed that there may be a possible association 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 be associated with ischemic stroke. This is supported by the results in Vyas and co-workers (2012) that reported a potential increased risk of 5 % for shift workers (Vyas et al. 2012) and systematic review reporting that epidemiological evidence for an association between shift work and ischemic stroke was limited (Jakobsson and Gustavsson 2013). Vyas and
co-workers 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, Vyas and co-workers (2012) excluded the broader definition cerebrovascular disease. This was preferable given that the risk factors associated with ischemic stroke are more similar to the risk factors associated with IHD (O'Donnell et al. 2010). This was supported in a systematic review, where the authors concluded that the possible causal relationship between ischemic stroke and shift work was accentuated by the association between known risk factors for CVD and shift work (Jakobsson and Gustavsson 2013).

One circumstance that could have influenced the results in paper I was the fact that average age of a patient with ischemic stroke is 75.6 years (Riksstroke 2015), and most of the participants included in the analyses 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.

To summarise, shift work may be associated with ischemic stroke but the excess risk is small. This is probably explained by the fact that ischemic stroke often occur in persons older than what MI do.

**Shift work and case fatality (paper II)**

The results from 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 largely.

Adjusting for high blood pressure 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 high blood pressure were not assessed in this analysis due to lack of such data for cases included in the data set.

The result that female shift workers not had an increased risk for case fatality compared with female day workers needs to be elaborated in future studies. The labour market is gender segregated in Sweden with more women in, e.g. the health care sector and more men in, e.g. the transport sector (Statistics Sweden 2012), and that means that the working situation for women and men in shift work compared with day work could be different. Paper II reports a case fatality among male shift workers of 21.2 % and male day workers of 14.3 %. For females, the corresponding case fatality for shift workers was 13 % and for day workers 21.2 %. Male shift workers and female day workers in this study have relatively similar case fatality compared to other Swedish reports, while the case fatality for male day workers and female shift workers are lower in comparison (Rosengren et al. 2001). The low case fatality for female shift workers may be related to a small actual number of fatalities.

From 1978 to 2008, there is a trend in Sweden of decreasing case fatality rates after first time MI, for both men and women (Yang et al. 2012). Repeating this study using a dataset reflecting the working conditions in Sweden 2015, the results would likely indicate lower case fatality rates for both shift workers and day
workers. But, the relative difference in case fatality risk of MI reported for male shift workers compared with male day workers in this study is likely to be relevant as of today even though the absolute risk has decreased.

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 (Vyas et al. 2012), the selected outcome variables e.g. IHD compared to CVD could potentially have contributed to a 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 (Vyas et al. 2012). 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 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 associated with shift work such as tobacco smoking (van Amelsvoort et al. 2006). 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, case fatality of MI is elevated, it is likely to have some effect on their total mortality. This will warrant caution of MI cases with shift work exposure, which in term can reduce the overall CVD mortality and act as a foundation for prevention of case fatality.

**Shift work and risk factor interaction (paper III)**

The results of paper III showed that shift work and physical inactivity interacted for males, and high WHR or elevated triglycerides interacted with shift work for females and their risk of MI.

The results indicate that the negative consequences of physical inactivity may be more hazardous for male shift workers compared to male day workers regarding the risk of MI. It has been previously reported that leisure-time physical activity is associated with decreased risk of CVD (Li and Siegrist 2012) and lower prevalence of for example high blood pressure (Huai et al. 2013) and dyslipidaemia (Mann et al. 2014). Several mediating mechanisms by which physical activity is supposed to affect the risk of CVD have been proposed, such as raised HDL-cholesterol levels and thereby likely decreasing low density lipoprotein (LDL) cholesterol and triglycerides (Li and Siegrist 2012), improved insulin sensitivity (Mann et al. 2014), and thereby decreasing the risk of diabetes type II. Regular physical activity lowers C-reactive protein (CRP) levels and reduces inflammation (Holtermann et al. 2012) and thereby decreasing the risk of CVD. Some of the inflammatory lowering effect may be mediated by the lower body weight associated with regular exercise, as obesity and adipose tissue increase the inflammatory processes in the body. Thereby, an increase in physical activity for male shift workers may decrease their risk of MI. Promoting healthy life style choices among shift workers, such as decreased tobacco smoking, will also have other positive health effects.
High WHR and elevated triglycerides interacted with shift work among women, on the association with MI. It appears that these risk factors for MI are more harmful to female shift workers compared to day workers. Higher prevalence of high WHR among male shift workers has previously been reported (Nakamura et al. 1997). High WHR can indicate visceral adipose tissue that in turn is also a component in the metabolic syndrome and associated with increased risk of CVD (Grundy et al. 2004), and the metabolic syndrome is associated with shift work (F. Wang et al. 2014). High WHR and elevated triglycerides have also been shown to be associated with increased risk of MI and all-cause mortality among women (Lindquist et al. 2002; Lindqvist et al. 2006). The effects of elevated triglycerides for older women have been suggested to be associated with increased triglyceride rich LDL, that may have atherosclerotic effects. This could be related to a underlying age-related decrease in lipid metabolism (Lindquist et al. 2002). There is a need for further research to understand if there is an interaction between shift work and an age-related decrease in lipid metabolism among women.

Promoting physical activity among shift working women would potentially decrease their risk of CVD by reducing their visceral adipose tissue (Vissers et al. 2013). Triglyceride levels is likely to also be decreased via increased physical activity (Li and Siegrist 2012). Such efforts may counteract the interactions reported in this study for female shift workers. However, both male and female shift workers had a higher prevalence of diabetes type II than day workers did. But there were no interaction with shift work on the association with the risk of MI found in the analyses.

In a previous analysis of interactions between shift work and CHD, Tenkanen and colleagues (1998) used a sample of males employed within manufacturing industries. They reported that shift work together with cigarette smoking or high
BMI interacted on the risk of CHD (Tenkanen et al. 1998). They did not come to similar results regarding those risk factors. The methods for interaction assessment differ, they reported the RR of each of the four exposure scenarios, but did not calculate SI or similar outcome measure. Thereby, they did not analyse interaction as a departure from additivity. Excluding women and other types of shift work related occupations made their findings less representative of shift workers in general. Virkkunen and co-workers (2006) did not study any of the same included risk factors as in paper III (Virkkunen et al. 2006).

The labour market in Sweden is gender segregated. More women are employed in, e.g. the health care sector and more men in e.g. the transport sector, creating differences in work related exposures (StatisticsSweden. 2012). This may have affected the results in paper III, if male shift workers are exposed to for example toxic exposures and female shift workers to psychosocial stressors.

In the existing literature, only a limited number of studies have analysed interactions for shift work with other risk factors and the risk of MI. Therefore, more research in the field is needed. It might be that traditional risk factors are more hazardous for shift workers. If this is the case, ordinary confounder control such as stratification or logistic regression analysis without the use of interaction terms would not be enough to control for the traditional risk factors, and uneven distribution between cases and controls of risk factors would therefore not be sufficiently accounted for.

For further studies of interaction between shift work and the risk of CHD, it would be of interest for example to study indicators of vascular specific inflammation (Rudolf and Lewandrowski 2014). That could bring more understanding to the causes behind the association between shift work and CVD. If vascular inflammation and, for example physical inactivity, interacts with shift work, the
need for effective preventive measures would be even more highlighted given the potential increased risks of CHD.

In summary, paper III showed an interaction between shift work and physical inactivity and an increased association with risk of MI for males. Interactions were found for females between shift work and elevated triglycerides, WHR and an increased association with the risk of MI, indicating that these risk factors may be more harmful to male and female shift workers. The reported interactions suggest that focus on prevention among shift workers should aim at promoting physical activity and healthy life style choices in general.

**Shift work and heredity (paper IV)**

The results of paper IV showed an interaction between paternal history of MI or SCD and shift work for males and the risk of MI. No other similar studies were found.

Previous studies have shown that parental history of CVD is an independent risk factor for CVD outcomes (Weijmans et al. 2015). Different mechanisms for this association have been discussed, parental history of CVD accumulate both known and unidentified environmental and heritable risk factors in a specific family (de Goma et al. 2012). It has also been proposed that parental history of premature CVD accelerates accumulation of coronary artery calcium (Pandey et al. 2014).

The result of this study may not only be a result of biological inheritance. Factors related to sedentary life style such as obesity have been shown to proceed from generation to generation (Whitaker et al. 1997) the same has been shown to some extent for type of occupation (van de Mheen et al. 1998). An increased biological predisposition for MI and the inheritance of sedentary life style may explain the findings. Therefore, it may also be of interest to extend further analyses to
comprehend parental MI or SCD, in not only biological parents and potential interactions with shift work and the risk of CVD. There are findings showing an added value of extending the term ‘family history of CVD’ to comprehend factors such as age at onset of disease, type of family relationship and the number of affected relatives (van Daele et al. 2013). So-called early life events, exposures during infancy and childhood, may also play a role in our findings. A review from 2008 concluded that birth weight as an indicator of fetal nutrition has a U-shaped risk for the development of metabolic disease later in life (Gluckman et al. 2008).

Socioeconomic status in childhood is often directly related to the socioeconomic status of the parents. Childhood socioeconomic status has been associated with poorer adult health and health related behaviour (van de Mheen et al. 1998). Early life events and childhood socioeconomic status may interact with parental history of CHD. Such interactions could hold part of the explanation behind the results in this study.

A family history of diabetes among shift workers has been associated with an increased risk for the offspring to develop diabetes (Kawakami et al. 1999), showing that shift workers are at risk of getting the same health problems as their parents. Altogether, this would make an interesting aim for future studies that could bring understanding to the potential interplay between genetic factors and behavioural patterns leading up to increased risk of CHD.

No interaction between shift work and premature MI or SCD was found. Premature occurrence is often viewed as a vital component of the familial aggregation of CVD risks (Pandey et al. 2014).

Analysis of interactions between parental history of MI and SCD for females was excluded from this study due insufficient number of females in the study.
population. In order to analyse potential interactions between parental history of MI or SCD and shift work for females, larger study materials are needed.

To extend the hypothesis regarding interaction between parental MI or SCD and shift work, it would be interesting to conduct studies of interaction between parental incidence of a wider spectrum of CVD such as different forms of stroke (Seshadri et al. 2010), and also metabolic diseases like diabetes type II (Wikner et al. 2013). Such studies could further elucidate whether there are genetic- and environmental risks interacting to increase the risk of MI for shift workers. It would also be of interest to study familial clustering of CVD, extending from parental CVD to include also CVD among siblings (Nielsen et al. 2013) and potential interactions with shift work. Such studies may also help to shed light on if there are specific interactions attributed to CVD occurring in the same generation and shift work. Studying interactions between parental history of CVD and shift work, as in paper IV, helps to show that the association between shift work and CVD is likely to be affected also by this risk factor.

To summarise; the findings in this paper show that there is an interaction between paternal MI or SCD and shift work on the risk of MI. These findings may have clinical implication for occupational health workers when assessing the future risk of MI for shift workers; paternal history of MI or SCD needs to be taken into account. By doing so, they will increase the possibility of finding employees with increased risk of MI. More research is needed to clarify potential interaction between shift work and parental history of MI or SCD.
**Study design considerations**

All papers were based on case-control studies, conducted by well-established research organisations, thereby accounting for presumably good data quality and thereby positively affecting the precision in the results.

**Questionnaire data**

There is a potential risk of misclassification, in study II, III and IV, 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. Study I was based on a nested case-control study where the outcome was unknown at the time of data collection.

Questionnaire data is subject to bias, both in the actual reporting from the respondent but also in so-called healthy worker survivor bias. 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 determining their working conditions correctly. This may lead to an underestimation of the risk associated with shift work exposure. Information about shift work or day work was based on questionnaire data, concerning the last five years of their working life. The questionnaire data regarding shift work exposure used in the SHEEP/VEEP study and the definition of shift- and day work derived from that question has been used in previous studies (Knutsson et al. 1999). It has been proposed that questionnaire data on shift work would not be subject to much recall bias (Kolstad 2008).

Healthy worker survivor bias is defined as the trend of unhealthy individuals leaving, for example shift work, earlier, and thereby receiving less exposure, in this case to shift work. This is likely to create a scenario were participants that remain in shift work may be less prone to different forms of diseases. Several methods have been suggested for controlling study outcomes for healthy worker survivor
bias, one being cohort restriction. Cohort restriction means that the exposure in question must have been present for a specified period, which was the case in papers I-IV (Buckley et al. 2015). Lifetime exposure to shift work is not possible to derive from the data, which represents a limitation.

In addition, there may be a need to further development in the granularity of the shift work exposure when derived from questionnaire data. By just using a one-dimensional shift work variable, the information about the length of shift work exposure will not be included. That may underestimate a potential dose-response effect in the length of shift work exposure.

Data on parental history of MI or SCD was also collected from questionnaire data. SCD was intended as a proxy for mortality related to a number of CVD associated with SCD, but may be subject to bias relating to the level of medical knowledge of the respondent, or to the age of the respondent at the time of the parents passing. At young age, the risk of misunderstanding the actual diagnosis that caused the mortality may be decreased, and if the event occurred at young age, the risk of recall bias increases if the questionnaire was completed later in life. Validation of such questionnaire data via the use of registries has been performed confirming the reliability of questionnaire data when analysing the association between parental MI increases the risk of MI in offspring (Nielsen et al. 2013).

**Clinical data**

In the papers in this thesis, two definitions of high blood pressure are used, ≥ 140 mmHg/≥ 90 mmHg or ≥ 170 mmHg/≥ 95 mmHg. This is primarily related to a change in the diagnostic cut-off level for high blood pressure over time. In the SHEEP/VHEEP study, initiated prior to the MONICA study, the cut-off level was higher. By using the low cut-off level, the effects of high blood pressure may have been attenuated by inclusion of participants with slightly elevated blood pressure,
thereby risking undervaluing the association between shift work and ischemic stroke. This scenario was relevant for paper II to IV.

Overweight was addressed as BMI ≥ 28. Even with the general acceptance of measuring overweight BMI > 25 (WHO 1995), there are findings showing that a BMI of somewhere between 25 to 28 may be associated with lower mortality compared to both higher and lower BMI for young women (Lindqvist et al. 2006). The cut-off levels have been questioned in relation to how the category of BMI between 25 to 30 predicts increased mortality for both males and females (McGee 2005). In old age, overweight and even obesity may have a protective effect on mortality, sometimes referred to as the obesity paradox. This may be related to the fact that this group is made up of individuals with different weight history. The group with the worst prognosis is those who were overweight as middle-aged and decreased their weight later in life (Strandberg et al. 2009). Thereby, using a BMI of 25 to 30 is rather complex in studies analysing mortality.

WHR has also been reported to be a better discriminant of cardiovascular risk factors than BMI (C. Lee et al. 2008). Even so, overweight is associated with CVD (Bogers et al. 2007) making a combination of BMI and WHR preferable when studying incidence of MI.

Given the association between shift work and the metabolic syndrome, supported in a number of studies, for example in a meta-analysis (F. Wang et al. 2014), it is vital to conduct further studies to gain more understanding of associations and interactions in this field. When doing so, high WHR in combination with a BMI ≥ 28 may be preferable to characterize overweight and obesity among shift workers.

It is vital, when conducting studies on the association between shift work and CVD on both males and females, to include both cholesterol and triglycerides given the
previously described gender/sex differences (Lapidus et al. 1985; Lindquist et al. 2002; Wilhelmsen et al. 1973). Future studies on blood lipids among shift workers may shed light on potential interaction effects that could explain associations between shift work and atherosclerosis (Haupt et al. 2008).

Interaction analysis
A number of epidemiologists have argued that so called biologic interaction should be assessed on an additive scale as in paper III and paper IV (Andersson et al. 2005; Hallqvist et al. 1996). The term biological interaction assumes some understanding of the underlying biological process behind the results; therefore, the term should be used with some caution. Interaction can be assessed both on an additive scale and on a multiplicative scale. The values for $A_1B_1$, $A_1B_0$ and $A_0B_1$ are provided in the results of paper III and paper IV so that the reader using the following formula can assess multiplicative interaction:

$$A_1B_1 = A_1B_0 \times A_0B_1$$

Multiplicative interaction is considered when:

$$A_1B_0 \times A_0B_1 < A_1B_1$$

Compared to additive interaction, multiplicative interaction does not consider the unexposed reference category ($A_0B_0$) and can provide results showing a higher interaction compared to the results from additive interaction calculated on the same data (Ahlbom and Alfredsson 2005).

A previous simulation study has questioned the use of measures of additive interaction calculated by substituting OR in place of RR reporting that they may not be reliable (Kalilani and Atashili 2006). OR only approximate the RR. When the
OR is more than 1, odds ratio tends to overestimate the RR (Davies et al. 1998). When analysing interaction between two risk factors using OR and using the RERI or SI, caution should be applied in conclusions about interactions, especially in studies with common outcomes. It has been shown that AP is likely to be more robust to when using OR in place of RR in interaction analyses (Kalilani and Atashili 2006). When analysing additive interaction and adjusting for covariates, SI has been proven to be more stable given that it does not vary across strata of the additional covariates (Skrondal 2003). It has been suggested that AP, SI and, RERI should be used when assessing additive interaction (Kalilani and Atashili 2006).

Confounding control was not addressed further in paper III and IV than age adjustment. Given that the potential interactions between confounders in relation to shift work and CVD are sparsely studied, the choice of potential confounders in interaction analyses is an area where further research is needed.

**Sex/gender in studies on shift work**

Many of the studies analysing associations between shift work and CVD, have been performed on male subjects, creating uncertainties to whether the associations found in the studies are applicable to females. It has been shown that established risk factors for CVD are associated with a higher relative risk for females than males (Reuterwall et al. 1999), further studies could show if the same results apply for shift work as a risk factor. In this thesis, females have been analysed in papers I to III, in paper IV females were excluded due to insufficient number of participants eligible for analysis.

**Sample size in studies on shift work**

A number of the cohort studies on the association between shift work and CVD have been performed on rather small cohorts, around 300 to 600 participants, this applies especially to older studies (Bertuzzi et al. 2003; Knutsson et al. 1986; Koller 1983; Rafnsson and Gunnarsdóttir 1990). The results in such studies could be
underpowered. In comparison, there are a number of cohort studies on the association between shift work and CVD that have been performed on large study materials (over 20,000 participants) (Alfredsson et al. 1985; Brown et al. 2009; Kawachi et al. 1995). The result from such studies are less likely to be underpowered and thereby of greater generalisability in comparison to smaller studies. Paper I and paper IV were performed on rather small data materials. Paper II and paper III were performed on data materials including 1,500 participants.

**Interpretation and implications**

Shift work was not associated with an increased risk of ischemic stroke. Thereby, it is likely to assume that the association between CVD and shift work is less associated with ischemic stroke and more 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), and by the fact that ischemic stroke in general occurs later in life (Riksstroke 2015).

Exposure to shift work is associated with increased risk of death within 28 days after MI for male shift workers. This finding may warrant increased caution of male shift workers treated in hospital with MI. 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.

Shift work interacts with CVD risk factors such as physical inactivity, high WHR, high triglycerides, and paternal history of MI or SCD. This indicates that these risk factors may be more hazardous to shift workers.
Given that shift work is common and increasing in prevalence 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.

**Need for further study**

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

- Prospective cohort studies of shift workers and non-shift workers with clarified disease end-points, to bring more light on the association between shift work and CVD.

- Most of the studies 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 is needed on female shift workers, both in order to clarify how shift work affects females and to create the possibility of assessing gender differences in risks associated with shift work.

- More research on potential biological mechanisms such as circadian disruption, sleep deprivation, and HRV is needed. This would bring more understanding to the association between shift work and CVD, especially with a focus on the association between shift work and the development of atherosclerosis.
• A more granular assessment of shift work exposure may improve the precision in the results; the same goes for a harmonisation of the analysed CVD outcome variables.

• It would also be of interest to explore whether there is a greater recall bias related to whether one has been exposed to shift work or night work.

• Given the association between shift work and CVD, it would be interesting to include shift work in risk assessment models such as the Framingham risk score for CVD.
CONCLUSION

In summary, the findings did not indicate a higher risk of shift workers developing ischemic stroke compared to day workers.

Male shift workers had an increased risk for case fatality within 28 days after MI; such results were not found for female shift workers.

Shift work interacts with some CVD risk factors indicating that the association between MI and shift work may in part be attributed to interactions between risk factors and shift work. This could mean that the specific risk factors are more harmful to shift workers compared to day workers.

The findings in this thesis bring further strength to the association between shift work and CVD, MI specifically. However, more research is needed to clarify and characterise these results.
ACKNOWLEDGMENTS

I would like to thank my two main supervisors, professor Anders Knutsson, professor Katja Gillander Gådin, and my co-supervisor associate professor Berndt Karlsson, to whom without this thesis never would have written or completed. They have in every way possible shared their deep knowledge within the field of epidemiology, shift work, and health.

In addition, I would like to thank Göran Fahlén, Hans Goine, and Maria Nordin for stimulating conversations during our meetings within the research group. Also, I would like to thank my co-workers and friends, such as Bengt Wramner, May Blom, Stefan, Anna and Daniel, Thomas and Loo-Anna. The same goes for the rest of my family in Olof, Lena, Kristian, Henrik, and to Gunilla and Fredrik.

Most importantly, I have to express my deepest gratitude to my fiancé and “fourth supervisor” Jeannette Olsson, for her everlasting support and devotion. Finally, Max, the embodiment of a bundle of joy.
REFERENCES


Alberti, K., et al. (2009), 'Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International', *Circulation*, 120, 1640-5.


Bogers, R. P., et al. (2007), 'Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons', *Arch Intern Med*, 167 (16), 1720-8.


Bøggild, H., et al. (1999), 'Shift work, social class, and ischaemic heart disease in middle aged and elderly men; a 22 year follow up in the Copenhagen Male Study', *Occup Environ Med*, 56 (9), 640-5.


Falger, PR. and Schouten, EG. (1992), 'Exhaustion, psychological stressors in the work environment and acute myocardial infarction in men', *J Psychosom Res*, 36 (8), 777-86.
Haupt, C. M., et al. (2008), 'The relation of exposure to shift work with atherosclerosis and myocardial infarction in a general population', *Atherosclerosis*, 201 (1), 205-11.
Kawachi, I., et al. (1995), 'Prospective study of shift work and risk of coronary heart disease in women', Circulation, 92 (11), 3178-82.


Lundberg, M., et al. (1996), 'A SAS program calculating three measures of interaction with confidence intervals', Epidemiology, 7 (6), 655-6.


McMurray, J. J., et al. (2012), 'ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology', *Eur Heart J*, 33 (14), 1787-847.


Nagaya, T., et al. (2002), 'Markers of insulin resistance in day and shift workers aged 30-59 years', *Int Arch Occup Environ Health*, 75 (8), 562-68.


---, (2015a), 'Socialstyrelsens statistikdatabas'.


Wang, T. J. (2008), 'New cardiovascular risk factors exist, but are they clinically useful?', *Eur Heart J*, 29 (4), 441-4.


Violanti, J., et al. (2009), 'Atypical work hours and metabolic syndrome among police officers', Arch Environ Occup Health, 64 (3), 194-201.

Virkkunen, H., et al. (2006), 'The triad of shift work, occupational noise, and physical workload and risk of coronary heart disease', Occup Environ Med, 63 (6), 378-86.


Yong, M., et al. (2014), 'Shift work and risk of non-cancer mortality in a cohort of German male chemical workers', Int Arch Occup Environ Health, 87 (7), 763-73.


Åkerstedt, T. and Wright, K. (2009), 'Sleep loss and fatigue in shift work and shift work disorder', Sleep Med Clin, 14 (2), 257-71.


68