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Shift work and cardiovascular risk factors

Prevention among airline employees

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ACADEMIC DISSERTATION

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Cover picture by Katriina Viitasalo

To my family and

late son and sister

Contents

List of original publications

This dissertation is based on two separate sets of data, the Health check-up data (studies I, II, IV, and V) and the Shift system change data (study III). The results have been reported in the following original articles listed by the aims of the thesis (page 54). In addition, some unpublished data are presented.

I. Viitasalo K, Lindström J, Hemiö K, Puttonen S, Koho A, Härmä M, Peltonen M.
Occupational Health Care identifies risk for type 2 diabetes and cardiovascular disease.
Primary Care Diabetes. 2012; 6(2):95-102.

II. Puttonen S, Viitasalo K, Härmä M.
The relationship between current and former shift work and the metabolic syndrome.
Scandinavian Journal of Work, Environment & Health. 2012; 38(4):343-348.

III. Viitasalo K, Kuosma E, Laitinen J, Härmä M.
Effects of shift rotation and the flexibility of a shift system on daytime alertness and cardiovascular risk factors.
Scandinavian Journal of Work, Environment & Health. 2008. 34(3):198–205.

IV. Viitasalo K, Puttonen S, Kuosma E, Lindström J, Härmä M.
Shift rotation and age - interactions for sleep-wakefulness and inflammation.
Ergonomics. 2014 Oct 17:1-10.

V. Viitasalo K, Hemiö K, Puttonen S, Leiviskä J, Hyvärinen H-K, Härmä M, Peltonen M, Lindström J.
Prevention of diabetes and cardiovascular diseases in Occupational Health Care: Feasibility and effectiveness.
Primary Care Diabetes. 2015 Apr; 9(2):96-104.

Abbreviations

BMI	Body mass index
BNSQ	Basic Nordic Sleep Questionnaire
CHD	Coronary heart disease
CVD	Cardiovascular disease
DPS	Diabetes Prevention Study
DPP	Diabetes Prevention Program
ESS	Epworth Sleepiness Scale
FINDRISC	Finnish Diabetes Risk score
FHS	Finnair Health Services
fP-gluc	Fasting plasma glucose
HbA1c	Glycosylated hemoglobin
HDL	High density lipoprotein cholesterol
HR	Hazard ratio
hsCRP	High-sensitivity C-reactive protein
IHD	Ischemic heart disease
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IPAQ	Physical Activity Questionnaire
LTPA	Leisure time physical activity
LDL	Low density lipoprotein cholesterol
MetS	Metabolic syndrome
mmHg	Millimeter of mercury
NCEP	National Cholesterol Education Program Expert Panel
OGTT	Oral glucose tolerance test
OHC	Occupational Health Care
OR	Odds ratio
RCGP	Royal College of General Practitioners
RR	Relative risk
T2D	Type 2 diabetes
WBC	White blood cell (leukocyte count)
WHO	World Health Organisation

Abstract

Epidemiologic evidence supports an association between shift work and increased risk of cardiovascular diseases. Shortened and disturbed sleep, circadian misalignment and alterations of environmental and lifestyle aspects are the main factors related to shift workers' health problems. Along with our modern 24/7 society, shift work and diverse working hours have become inevitable. In a globally operating airline, irregular working hours and time-zone flights are challenging to workers' coping strategies and their health, especially as they age.

The main purpose of this study was to evaluate the feasibility and effectiveness of screening and prevention of cardiovascular risk factors and type 2 diabetes among shift workers in a Finnish airline. Two kinds of interventions were tested to promote workers' cardiovascular health and abilities to cope with shift work; changes in shift systems and lifestyle counselling. This thesis encompasses two longitudinal datasets based on interventions among the employees of the airline; the data of the health check-up study (n=2312) and the data of the shift system change study (n=84).

Findings from the cross-sectional health check-up sub-data suggested that metabolic syndrome is more prevalent among former male shift workers than male day workers who have never worked shifts.

The results of the shift system change study, carried out in the line maintenance unit among male participants, indicated that a faster speed together with a change from the backward to forward direction in shift rotation alleviates daytime sleepiness. In addition, combining individual elements of work time control with company-based variability in a shift system can have favourable effects on shift workers' cardiovascular health markers. A decrease in systolic blood pressure in combination with a declining trend for heart rate could indicate a decrease in psychophysiological stress in the more flexible shift system.

In the analyses of the cross-sectional sub-data of the health check-up study, our earlier findings that a rapidly forward rotating shift system is more age-friendly for sleep compared to a backward and slower rotating three-shift systems was supported. Quickly forward rotation shift workers considered their working schedule to be less harmful to sleep and wakefulness compared to slower backward rotation shift workers. In the quickly forward rotating three-shift system older workers had less sleep complaints than their younger colleagues.

The renewed health check-up process effectively identified employees with increased risk of type 2 diabetes and cardiovascular diseases, the individuals who would benefit from lifestyle intervention. The

FINDRISC questionnaire proved to be a practicable first-step screening method in an occupational health care setting. The follow-up data of the health check-up study showed that low intensity lifestyle interventions are feasible in an occupational health care setting. However, only modest health benefits were observed among the men with increased risk. We probably identified the right target group for our interventions but greater health effects would have required more intensive and long-lasting interventions.

A number of factors are associated with participation in the lifestyle interventions. Employees with higher baseline FINDRISC score and clinical and lifestyle risk factors were eager to take part in lifestyle counselling by a dietician or a diabetes nurse. Also problems in sleep and mood increased attendance in the interventions. The factors associating with participation differed between genders in some aspects, which may reflect the different requirements and challenges of work and health. The men worked mainly in blue collar tasks, e.g. in technical, ground or cargo services, and the women mainly in white collar duties, e.g. in office or gate services and in-flight duties.

In conclusion, former shift workers' increased risk for metabolic syndrome should be recognized in occupational health care and taken into account in preventive work. In the design of new shift systems, a faster speed, together with the forward rotation of the shift system enhance older workers' well-being and coping strategies for shift work. In addition, combining individual-based flexibility with company-based working-time flexibility may have favourable effects on shift workers' cardiovascular health. Based on the health check-up study, even a low intensity lifestyle intervention that targets individuals at risk may be profitable. The work and individual related characteristics associated with participation in the lifestyle interventions, identified in this study, can probably be useful for developing more effective lifestyle intervention activities within occupational health care.

Keywords: shift work, shift schedule, cardiovascular disease, type 2 diabetes, risk factors, prevention, occupational health

Tiivistelmä

Epidemiologinen tutkimus tukee vuorotyön yhteyttä sydän- ja verisuonisairauksien riskiin. Univaje ja unihäiriöt, vuorokausirytmin häiriintyminen ja muutokset elinympäristössä sekä elintavoissa vaikuttavat vuorotyöntekijän terveyteen. Nykyinen 24/7-yhteiskunta ja monimuotoiset työajat ovat tulleet väistämättömiksi. Maailmanlaajuisesti operoivassa lentoyhtiössä epäsäännölliset työajat ja aikaerolennot ovat haasteellisia työntekijöiden jaksamiselle ja terveydelle, erityisesti ikääntymisen myötä.

Tämän väitöskirjatyön tarkoitus oli selvittää, onko sydän- ja verisuonisairauksien sekä tyypin 2 diabeteksen riskin seulonta ja ehkäisy toteutettavissa monimuotoisia työaikoja tekevien työntekijöiden keskuudessa ja onko se tehokasta. Tutkimuksessa testattiin kahta interventiota, vuorotyörytmin muutosta ja elintapaneuvontaa sydän- ja verisuonisairauksien riskitekijöiden ja tyypin 2 diabeteksen riskin vähentämiseksi sekä vuorotyössä jaksamisen edistämiseksi. Tämä väitöskirja sisältää kaksi pitkittäistä interventioaineistoa, jotka on kerätty suomalaisen lentoyhtiön työntekijöistä. Terveystarkastustutkimusta koskeva aineisto sisältää 2312 henkilön tutkimustiedot ja vuorotyörytmin muutosta koskeva aineisto 84 mieshenkilön tutkimustiedot.

Terveystarkastustutkimuksen poikkileikkausaineiston tulosten mukaan metabolinen oireyhtymä oli miehillä yleisempi päivätyöhön siirtyneiden entisten vuorotyöntekijöiden keskuudessa verrattuna niihin, jotka eivät olleet koskaan tehneet vuorotyötä.

Tekniikan linjahuollossa toteutettu vuorotyörytmin muutos hitaasti taaksepäin kiertävästä nopeasti eteenpäin kiertäväksi vähensi vuorotyöntekijän päiväväsymystä. Nopeasti eteenpäin kiertävään vuorojärjestelmään siirtyneet työntekijät arvioivat myös terveystarkastustutkimuksessa työaikansa häiritsevän vähemmän unta ja päiväaikaista vireystilaa kuin työntekijät, jotka jatkoivat työskentelyä hitaasti taaksepäin kiertävässä vuorojärjestelmässä. Terveystarkastustutkimuksen poikkileikkausaineiston tulokset vahvistivat aiempaa havaintoamme siitä, että nopeasti eteenpäin kiertävä vuorojärjestelmä on ikäystävällisempi verrattuna hitaammin ja taaksepäin kiertävään vuorojärjestelmään. Nopeasti eteenpäin kiertävässä vuorojärjestelmässä iäkkäämmillä työntekijöillä oli nuorempia vähemmän uniongelmia.

Vuorotyörytmin muutostutkimuksessa joustavampaan työvuorojärjestelmään siirtyneiden systolinen verenpaine laski ja pulssitaso laski lähes merkitsevästi viitaten psykofysiologisen stressin vähenemiseen, mikä saattaa vaikuttaa edullisesti vuorotyöntekijän sydänterveyteen.

Uudistettu terveystarkastuskäytäntö löysi tehokkaasti ne henkilöt, joiden tyypin 2 diabeteksen sekä sydän- ja verisuonisairauksien riski oli kohonnut ja jotka todennäköisesti hyötyisivät elintapaohjauksesta. Diabeteksen riskikysely FINDRISC osoittautui tässä käyttökelpoiseksi ensivaiheen seulontamenetelmäksi. Terveystarkastustutkimuksen seuranta-aineisto osoitti, että kevyt elintapaohjaus onnistuu työterveyshuollon terveystarkastusten yhteydessä. Kuitenkin tällaisella kevyellä interventiolla saatiin aikaan vain kohtalaisia terveyshyötyjä kohonneen riskin miehillä. Selvempien terveysvaikutusten saavuttamiseksi tarvitaan intensiivisempiä ja pitkäkestoisempia interventioita.

Tutkimuksemme paljasti joukon taustatekijöitä, jotka olivat yhteydessä interventioihin osallistumiseen. Työntekijät, joilla oli korkea diabetesriskipistemäärä ja joilla oli kliinisiä tai elintapoihin liittyviä riskitekijöitä, olivat innokkaampia hakeutumaan ravitsemusterapeutin ja diabeteshoitajan ohjaukseen. Myös uneen ja mielialaan liittyvät ongelmat lisäsivät interventioissa käyntiä. Miehet ja naiset erosivat jonkin verran näiden taustatekijöiden suhteen, mihin saattoi vaikuttaa sosioekonomiset erot ammattiryhmien välillä. Miehet työskentelivät pääasiassa tekniikassa, maapalvelussa ja rahdissa, kun taas naiset työskentelivät enimmäkseen toimistossa tai asiakaspalvelutehtävissä porttipalvelussa tai matkustamopalvelussa.

Vuorotyötä aiemmin tehneillä miehillä havaittu lisääntynyt riski sairastua metaboliseen oireyhtymään pitää tunnistaa ja pyrkiä ehkäisemään työterveyshuollossa. Tutkimuksemme vahvistaa tietoa, että nopeasti eteenpäin suuntautuva vuorokierto lisää yli 45 vuotiaiden työntekijöiden hyvinvointia ja jaksamista vuorotyössä. Joustava työaika, jossa työntekijä voi paremmin vaikuttaa työaikoihinsa, näyttäisi tutkimuksemme mukaan olevan edullinen vuorotyöntekijän sydänterveydelle.
Terveystarkastustutkimuksen mukaan korkean riskin miehet saattavat hyötyä vähäisestäkin elintapaohjauksesta, joskin selvempien terveysvaikutusten saamiseksi tarvitaan intensiivisempiä ja pitkäkestoisempia interventioita. Tutkimuksessa havaittuja osallistumiseen vaikuttavia taustatekijöitä voidaan hyödyntää työterveyshuollossa toteutettavan elintapaohjauksen suunnittelussa.

Avainsanat: vuorotyö, vuorojärjestelmät, sydän- ja verisuonisairaudet, tyypin 2 diabetes, riskitekijät, ennaltaehkäisy, työterveyshuolto

1. Introduction

“The right to work in safety is a basic human right, and protection of the health of workers is ultimately of benefit to all of society” states the editorial of PloS Med in June 2007 (Barbour et al. 2007).

Epidemiologic and experimental evidence supports the plausible association between shift work and an increased risk of cardiovascular disease (CVD), even though the exact mechanisms for this association are not firmly established. Shift work has also been associated with metabolic disorders such as obesity (Poulsen et al. 2014), metabolic syndrome (MetS) (Kawada and Otsuka 2014; Pietroiusti et al. 2010; F. Wang et al. 2014), and type 2 diabetes (T2D) (Gan et al. 2015; Pan et al. 2011). In addition, many other health-related problems, such as gastrointestinal, psychological, and female reproductive health disorders, have been linked to shift working (Costa 2010; Costa et al. 2010; Knutsson 2003). The International Agency for Research on Cancer has classified night work as a "probable human carcinogen" (Straif et al. 2007). Evidence of the association between shift/night shift work and mortality is limited and inconsistent (Akerstedt et al. 2004; Karlsson et al. 2005; Knutsson 2004; Taylor and Pocock 1972; X. S. Wang et al. 2011). However, in the Nurses' Health Study, 22 years of follow-up revealed that women working rotating night shifts for 5 years or more had a modest increase in all-cause and CVD mortality (Gu et al. 2015).

Shortened or disturbed sleep, circadian misalignment and alterations of environmental and lifestyle aspects are the main factors related to shift workers’ health problems. The plausible physiological and biological mechanisms are related to the activation of the autonomic nervous system, inflammation, changes in lipid and glucose metabolism, and related changes in the risk for atherosclerosis, metabolic syndrome, and type 2 diabetes (Puttonen et al. 2010; Zimberg et al. 2012). Along with our modern 24/7 society shift work and diverse working hours have become inevitable, thus, the option of eradicating exposure to shift work completely is not realistic. Shift work is carried out by 17% of workers across the EU and in this regard there are no gender differences. Fulltime workers do more shift work than part-time workers and younger workers more often work shifts than older workers ("5th European Working Condition Survey " 2012). One third of Finnish salary-earners do not have a regular day work and one worker in five works in two or three shifts or only during the night ("Quality of Work Life Survey 2013, Statistics Finland" 2014). Finnish legislation defines night work as a specific health risk and statutory regular health check-ups are obligatory for night shift workers.

Globally, non-communicable diseases are the leading cause of mortality, cardiovascular diseases comprising up to 46% of these deaths ("World Health organization" 2014). In Europe, cardiovascular diseases have shown a significant decline in recent decades. In 2009, coronary heart disease rates in younger adult age groups as well as in the population overall were less than half of what they had been in the early 1980s (Nichols et al. 2013a, 2013b). In Finland, between the years 1972 and 2007 coronary mortality declined 80% in the middle-aged population, mainly due to a great reduction in conventional risk factor levels (e.g. cholesterol, blood pressure, and smoking). This risk factor change in turn has been associated with long-term chronic disease prevention and health promotion interventions (Vartiainen et al. 2010). Nonetheless, CVD still remains the main cause of morbidity and mortality and places a substantial burden on health care systems and national economies worldwide and, as such, more efficient intervention strategies are needed (Guazzi et al. 2014; Oliveira et al. 2015; "World Health organization " 2007). While secondary prevention is essential for high risk individuals after a cardiovascular event/diagnosis, primary prevention is potentially effective and worthwhile at the population level. In this context, workplace health promotion is viewed as a potential resource for further reducing the CVD burden (Arena et al. 2013; Guazzi et al. 2014).

In Finland occupational health care (OHC) is an important part of the primary health service system. Covering over 90% of the national workforce ("Work and Health in Finland, 2012" 2013) Finnish OHC has an excellent opportunity to influence the health of the working population. The traditional duty of OHC has been the prevention of work-related illnesses and injuries and health examinations have focused on workers' exposure to work processes and other occupational threats to working capacity. The role of OHC in health promotion, evaluation of individual health risks and also prevention of lifestyle related chronic illnesses has been emphasized by the Finland's Ministry of Social Affairs and Health. The Finnish development strategy for occupational health care outlines the measures for promoting employees' health and working capacity ("Government resolution. Occupational Health 2015 " 2004).

Lifestyle factors, like physical activity and dietary habits, are components in the pathway to metabolic syndrome, diabetes, and cardiovascular disease. These individual lifestyle-related risk factors of CVD are potentially amenable to intervention. As cardiovascular diseases and type 2 diabetes share common risk factors, initiatives to prevent CVD and T2D support each other.

Though some of the effects of shift work are unavoidable, such as the partial disruption of circadian rhythms, proper changes in certain shift characteristics or shift schedules may ameliorate shift workers' sleep and health. For instance, rotating shift work comprises a range of alternative schedule patterns where the shift system may rotate faster or slower, backward or forward and the length of shifts, as well as, the proportion of night and early morning shifts varies, and modifications to these shift work components might modify the health risks of shift work.

The employees of a large Finnish airline, Finnair, place special demands on shift work healthcare as most of them are shift workers. In addition, their duties involve matters of aviation safety that require the employees are of good health and very vigilant. In a globally operating airline, the numerous working hours and time-zone flights are challenging to workers' coping strategies and health especially as they age. The strict health standards required by the aviation authority make health promotion and the prevention of work and lifestyle related diseases even more important. The present work which includes interventions focusing on both working times and workers' lifestyles is in line with both the national health strategy and the airline's health policy.

2. Review of the literature

2.1 Shift work

“Shift work was not a consequence of the industrial revolution – the monks of the monastery, guards at the castle, and seafarers have been at work at odd hours since biblical times”, writes Henrik Boggild in his thesis (Boggild 2000). Shift work is common in our contemporary 24/7 societies as well as in developing countries where a considerable contingent of the populations work in shifts.

2.1.1 Concept of shift work

Shift work is an ambiguous term and there is no agreement on a definition for shift work in the literature. Collins English Dictionary defines shift work as ‘a system of employment where an individual's normal hours of work are, in part, outside the period of normal day working and may follow different patterns in consecutive periods of weeks’ (Collins 2012). The EU’s Working Time Directive defines shift work as 'any method of organising work in shifts whereby workers succeed each other at the same work station according to a certain pattern, including a rotating pattern, and which may be continuous or discontinuous, entailing the need for workers to work at different times over a given period of days or weeks'. Working hours across time zones are not specifically included in the definitions of shift work.

Shift work researchers use different definitions, which may impede comparisons of exposure and the results of studies. If the term ‘shift work’ is used as being synonymous to irregular or odd working hours and ‘a shift worker’ defined as anyone working outside regular daytime hours, shift workers include all people working evening shift, night shift, rotating shifts, split shifts or on-call or casual schedules, 24 hour shifts, irregular schedules, and other non-day schedules both during the week and on weekends (Szosland 2010; Vyas et al. 2012).

2.1.2 Different shift schedules and working time patterns

In the 24/7 society, a considerable portion of workers are engaged in non-standard working hours. The increasing diversification of working time patterns reflects societal reasons, as well as economic demands and individual preferences. On the one hand, companies look for a prompt adaptation of production and service systems to increasing market demands and technological innovations; while on the other hand, employees ask for a more balanced pattern between working and leisure times to improve their working and social lives (Costa 2003).

Shift systems can differ widely with respect to their structure; the presence/absence of night work; the duration of the duty period (e.g. from 6 to 12 h); the number of workers/crews who cover the whole working time (two, three, four or more teams); the interruption of the weekend (continuous/discontinuous); workers stay on a given shift, or alternate between the different shifts (permanent /rotating); the speed (fast/slow) and the direction (clockwise/counter-clockwise) of the shift rotation; the start and finish times of the duty periods; and the regularity/irregularity and length of the shift cycle (Costa 2003).

Among the various possible shift systems, alternating day (morning and afternoon) shifts are the most frequently used. Finland's Work Life Survey 2013 ("Quality of Work Life Survey 2013, Statistics Finland" 2014) reveals that among paid employees aged 15–64 (n=4,876), 68.3% were regular day workers (06:00 - 18:00), 0.7% only worked evenings, 0.9% only worked nights, 10.5% did 2-shift work not including night work and 1.9% did 2-shift work including night work, 6.3% did 3-shift work, and the rest 11.3% had other kinds of work times. In 2010, night work (working for at least two hours between 22:00 - 05:00) was undertaken by 19% of the EU workforce, men more often (23%) than women (14%). One in ten workers did night work more than five times a month. One worker in five (21%) worked 'on call', men (23%) more often than women (16%). More than half of all workers worked for at least one weekend day. Globally, shift work is even more common and for example up to 36% of the Chinese workforce worked in shifts in 2004 ("5th European Working Condition Survey " 2012).

2.2 Cardiovascular disease

The term cardiovascular disease refers to a range of conditions and disorders that affect the heart and blood vessels and includes, inter alia, coronary heart disease, cerebrovascular disease, raised blood pressure, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure. Atherosclerosis is the underlying pathology of cardiovascular diseases such as coronary artery disease (e.g. heart attacks), cerebrovascular disease (e.g. stroke) and diseases of the aorta and arteries (e.g. hypertension) ("World Health organization " 2007). Atherosclerosis is a complex pathological process in the walls of blood vessels. Factors that promote the atherosclerotic process are known as CVD risk factors. According to the World Health Organization over three-quarters of all CVD mortality may be prevented with adequate changes in lifestyle (Perk et al. 2012). The following sections discuss the most central factors, health disorders and diseases associated with the increased risk of CVD.

2.2.1 Conventional risk factors

Some traditional cardiovascular risk factors, such as age, gender, and heredity are unavoidable. However, avoidable behavioural and metabolic risk factors play key roles in the aetiology of atherosclerosis. The leading CVD risk factor is elevated blood pressure to which 13 per cent of global deaths are attributed, followed by tobacco use (9%), raised blood glucose (6%), physical inactivity (6%) and being overweight or obesity (5%)("World Heart Federation " 2012). A multicentre, international, case–control study (the INTERHEART study) defined nine potentially avoidable risk factors that account for over 90% of the risk of the first acute myocardial infarction. These include by decreasing odds ratio: raised apolipoprotein B/A1 ratio (3.25), current smoking status (2.87), psychosocial factors (2.67), diabetes (2.37), history of hypertension (1.91), abdominal obesity (1.12), alcohol consumption (0.91), regular physical activity (0.86), and daily consumption of fruits and vegetables (0.70) All these factors being significantly associated with acute myocardial infarction ($p<0.0001$ for all risk factors and $p=0.03$ for alcohol). Furthermore, the associations were consistent in both genders and different ethnicities and geographic regions, enhancing the worldwide generalizability of the results (Yusuf et al. 2004). The INTERSTROKE study, another multicentre case-control study, identified ten modifiable risk factors that explained approximately 90% of the risk for developing a first stroke, with hypertension being the most important. Nine risk factors were the same as in the INTERHEART study, added by cardiac causes of stroke (atrial fibrillation or flutter, previous myocardial infarction, rheumatic valve disease, or prosthetic heart valve) (O'Donnell et al. 2010).

2.2.2 Type 2 diabetes

Subjects with type 2 diabetes have a CVD risk comparable to that of previous myocardial infarction and the risk is greater in women (Haffner et al. 1998; Rivellese et al. 2010; Russo et al. 2015). Diabetes mellitus increases the risk of cardiovascular disease by three to four times in women and two to three times in men, after adjusting for other risk factors (Norhammar and Schenck-Gustafsson 2013). The most important avoidable risk factors for T2D are unhealthy diet, a sedentary lifestyle, and obesity (Hu et al. 2003; Lindstrom, Peltonen, et al. 2006; "World Health Organisation " 2003). Gradual weight gain during adult years is a common phenomenon. In longitudinal population studies (Nooyens et al. 2009; Pajunen et al. 2012; Piirtola et al. 2016) weight increased annually 0.2 to 0.7 kg among men and 0.2 to 0.6 kg among women. In the Helsinki Health Study, shift work that included night shifts was associated with increased risk of weight gain among women (OR 1.43 [95% CI 1.13, 1.82]) (Roos et al. 2013). Abdominal obesity is a more important risk factor than overall obesity in predicting the development of type 2 diabetes and cardiovascular disease (Siren et al. 2012).

In Western countries half of the T2D cases are estimated to be undiagnosed. In a Finnish population-based survey, previously undetected cases of type 2 diabetes were found in 9.3% of men and in 7.3% of women. In the age groups 45-54 and 55-64 years, 5.9% and 8.7% of men and 2.5% and 8.0% of women, respectively, suffered from undetected diabetes. (Saaristo et al. 2008). It has been estimated that the prevalence of total diabetes (diagnosed and undiagnosed) in the United States will increase to between 20% and 30% of adults by 2050 (Boyle et al. 2010; Narayan et al. 2006). The WHO projects that diabetes will be the 7th leading cause of death in 2030 ("World Health organization" 2014). This scenario highlights the large economic burden of diabetes (Yang et al. 2013) and underscores the importance of prevention.

2.2.3 Metabolic syndrome

Metabolic syndrome, first described by Reaven in 1988 (Reaven 1988), is a cluster of interrelated cardiovascular risk factors known to predispose to the development of T2D and CVD. Meta-analyses have strongly suggested that metabolic syndrome is an important risk factor for cardiovascular disease incidence and mortality, as well as all-cause mortality (Galassi et al. 2006; Gami et al. 2007; Mottillo et al. 2010). The clinical significance of MetS is its ability to identify individuals at risk from T2D and CVD for preventive treatments. However, it predicts these diseases less effectively than established predicting models such as the Diabetes Risk Score and the Framingham Risk Score (Stern et al. 2004).

There are many definitions of MetS e.g. provided by the Third Report of the National Cholesterol Education Program Expert Panel (NCEP-ATPIII) (Grundy et al. 2005), the International Diabetes Federation (IDF) (Alberti et al. 2005), the World Health Organization (WHO) (Alberti and Zimmet 1998), and the European Group for the Study of Insulin Resistance (EGIR) (Balkau and Charles 1999). Insulin resistance, hypertension, elevated triglyceride levels, and central obesity are included in all these definitions. Decreased HDL cholesterol is included in the WHO and IDF definitions and microalbuminuria only in the WHO definition. None of them include age and smoking, two main risk factors of CVD. A comprehensive comparison between the different definitions has been compiled by Huang (Huang 2009). It has been suggested that population and country specific cut points for waist circumference for defining abdominal obesity should be used (Alberti et al. 2009). The most used definitions are compiled in Table 1.

Table 1. Definitions of the metabolic syndrome according to the National Cholesterol Education Program (NCEP), the World Health Organization (WHO), and the International Diabetes Foundation (IDF).

	WHO (1998)	NCEP ATP III (2005)	IDF (2005)
Absolutely required	IR	None	Central obesity
Additional criteria	Two of the five criteria below	Any three of the five criteria below	Two of the four criteria below
Central obesity	Waist/hip ratio: M >0.90 F >0.85 or BMI >30	Waist: M >102cm F >88cm	Waist: M ≥ 94cm F ≥80cm
Hyperglycaemia	IR	F-gluc ≥ 5.6 mmol/l or Rx	F-gluc ≥ 5.6 mmol/l or T2D
Dyslipidaemia	Tg ≥ 1.7 mmol/l and/or HDL, M < 0.9 mmol/l F < 1.0 mmol/l	Tg ≥ 1.7 mmol/l or Rx	Tg ≥ 1.7 mmol/l or Rx
Dyslipidaemia (second separate criteria)		HDL M < 1.0 mmol/l or Rx F < 1.3 mmol/l or Rx	HDL M < 1.0 mmol/l or Rx F < 1.3 mmol/l or Rx
Elevated blood pressure	≥ 140/≥ 90 mmHg	≥ 130/≥ 85 mmHg or Rx	≥ 130/≥ 85 mmHg or Rx
Other	Microalbuminuria ≥ 20 ug/min		

BMI body mass index, F female, F-gluc fasting glucose, HDL high density lipoprotein, IR insulin resistance (impaired glucose tolerance; impaired fasting glucose; type 2 diabetes), M male, Rx pharmacologic treatment, Tg triglyceride, T2D type 2 diabetes.

2.2.4 Insufficient sleep and sleep disturbances

Experimental and epidemiologic studies have indicated that the quantity and quality of sleep predict weight gain, obesity, and type 2 diabetes (Cappuccio et al. 2010; Patel and Hu 2008; Spiegel et al. 2005; Trenell et al. 2007; H. Tuomilehto et al. 2008). Sleep deficiency and circadian disruption may contribute to these health disorders potentially by altering the timing and amount of food intake, disrupting energy balance, inflammation, and impairing glucose tolerance and insulin sensitivity (Depner et al. 2014). Self-reported insufficient sleep has effects on blood pressure, glucose metabolism, hormonal regulation, and inflammation altering these established cardiovascular risk factors in a direction that is known to increase the risk of cardiac morbidity (Mullington et al. 2009). In the Framingham Study, difficulty falling asleep was one of the predictors of myocardial infarction and coronary death among women (Eaker et al. 1992), and in a prospective Norwegian cohort study, insomnia associated with a moderately increased risk for acute myocardial infarction in both genders (Laugsand et al. 2011). In the Nurses' Health Study, both short and long self-reported sleep durations were independently associated with a modestly increased risk of coronary events among women (Ayas, White, Manson, et al. 2003). In a systematic review and meta-analysis of 474,684 participants (follow-up 6.9–25 years), a short self-reported duration of sleep (≤5–6 h per night) was associated with a greater risk of developing or dying of CHD and stroke (RR 1.5 and 1.1, respectively) and a self-reported long duration of sleep (8–9 h per night) with a greater risk of developing or dying of CHD, stroke, and total CVD (RR 1.4, 1.7, and 1.4, respectively) (Cappuccio et al. 2011).

2.3 Shift work and cardiovascular risk

Shift work has been linked to a number of adverse health effects such as an increased risk of obesity (Morikawa et al. 2007; Poulsen et al. 2014; Roos et al. 2013; Suwazono et al. 2008), metabolic syndrome (Kawada and Otsuka 2014; Pietroiusti et al. 2010; F. Wang et al. 2014), and type 2 diabetes (Gan et al. 2015), all of which predispose to cardiovascular diseases. The prevalence of risk factors for coronary heart disease is higher among shift workers compared to day workers (Peplonska et al. 2014; Ramin et al. 2015), and subjects with coronary risk factors are probably more likely to be affected by shift work (Fujino et al. 2006; Tenkanen et al. 1998; van de Ven et al. 2014). Shift working includes elements of work stress (Boggild and Knutsson 1999; Peter et al. 1999), and work stress has been associated with insufficient sleep and impaired recovery (Akerstedt 2006; Jacobsen et al. 2014), activation of the autonomic nervous system (Jarczok et al. 2013), and inflammatory responses (Johnson et al. 2013). All these may act as pathways from the circadian stress of shift work to cardiovascular morbidity as depicted in Figure 1 (Harma, Kompier, et al. 2006; Puttonen et al. 2010).

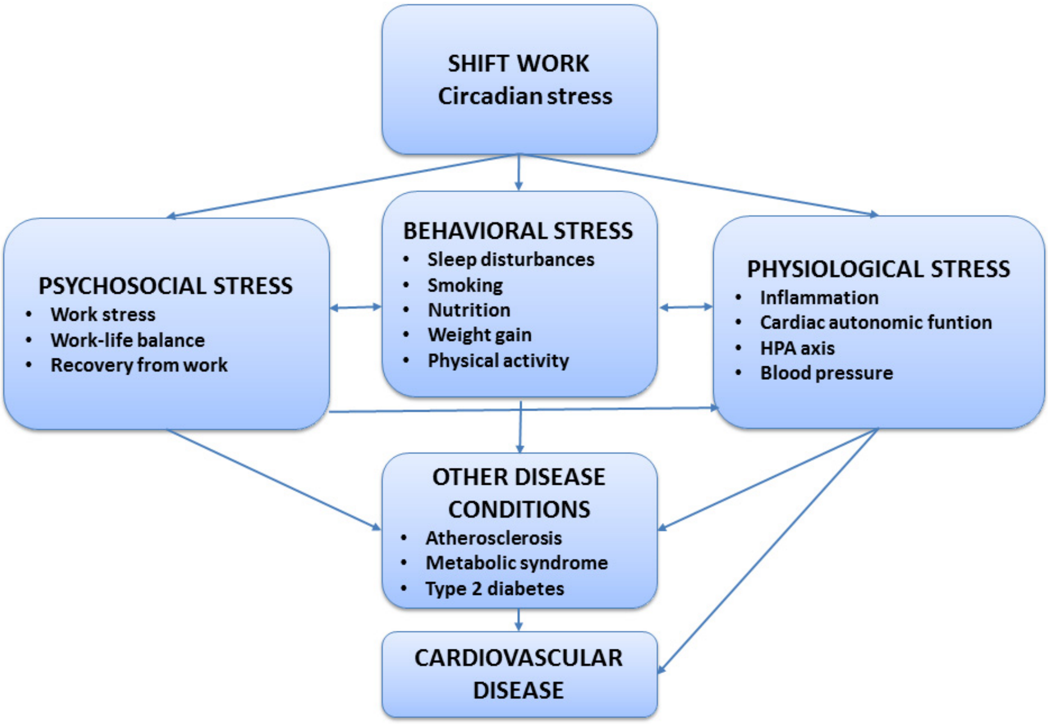

Figure 1. Pathways from shift work to cardiovascular disease (Modified from Puttonen et al. SJWEH 2010, vol 36, no 2).

2.3.1 Shift work and CVD

Epidemiologic and experimental research evidence supports a plausible, but not conclusive or systematic causal association between shift work and cardiovascular diseases. The evidence of the latest meta-analysis and reviews as well as some representative original cohort and case-control studies of this issue are compiled in Tables 2 and 3.

Table 2. Original studies on the association of shift work with cardiovascular risk and risk factors.

Reference	Study design	Participants	Time period	Shift work definition	Control group	Outcomes	Adjusted covariates	Results
Karlsson et al., 2005	Retrospective study from a Swedish cohort in the pulp and paper industry, linked to the national Cause of Death Register	2354 shift workers	1952 to 2001	Mainly rotating three-shift schedule	3088 day workers	Total mortality and mortality from coronary heart disease, stroke, and diabetes		Increased mortality from CHD, duration of shift work increased the risk. A trend of increased mortality from diabetes and stroke
Fujino et al., 2006	Prospective study from a Japanese Collaborative Cohort Study for the Evaluation of Cancer Risk	110,792 inhabitants Analyses on 17,649 full-time working men, free of MI and cerebrovascular disease at baseline	1988 to 1990	Mainly night (fixed-night shift), or alternate night and daytime (rotating-shift work)	Mainly daytime	Total deaths, deaths from circulatory system disease, ischemic heart disease, and cerebrovascular disease	Smoking Alcohol intake Hypertension Diabetes Education Stress Hours of walking and exercise Type of job	Rotating SW associates with death due to IHD

Reference	Study design	Participants	Time period	Shift work definition	Control group	Outcomes	Adjusted covariates	Results
Puttonen et al., 2009	Cross-sectional study to examine the relationship between SW and subclinical atherosclerosis from the cohort of a prospective epidemiological Cardiovascular Risk in Young Finns study	712 men and 831 women Ages from 24 to 39 years	1980 to 2001	shift work (2- or 3-shiftwork or regular evening or night work)	Day work	carotid IMT and carotid plaque	Lipids Homocysteine hsCRP Age Low SES Job strain Smoking Diet Physical inactivity Alcohol BMI Waist Family history of CHD	Men: SW was associated with mean and maximum IMT and a 2.2-fold odds for carotid plaque Women: no association between shift work and carotid atherosclerosis indicators.
Thomas et al., 2010	Longitudinal study to examined associations between exposure to shift-work and risk factors for CVD from a 1958 British birth cohort at age 45	Cohort 18,558 Analyses on 7,839 subjects	1958 to 2003	Any SW: any employment ≥1/week outside 07:00-18:00 Evening SW: 18:00-22:00 Night SW: 22:00-04:00 Early morning SW: 04:00-07:00	Employment outside 18:00-07:00, not weekends	Lipids HbA1c CRP Fibrinogen Blood pressure Height, Weight BMI Waist	Smoking Alcohol Diet LAP	Night /early morning SW: Men: elevated levels of all other but BP and total cholesterol. Women: elevated triglyceride levels. Results of BMI, WC and CRP remained significant after adjustment Evening SW: Men: elevated BMI and total cholesterol

Reference	Study design	Participants	Time period	Shift work definition	Control group	Outcomes	Adjusted covariates	Results
Wang et al., 2015	Prospective cohort of Kuopio Ischemic Heart Disease Risk Factor Study	621 men Aged 42 to 60 years	1987 to 2000,	Weekend shifts Evening/night/ rotating shifts Other shift work	Standard daytime work	Change of carotid IMT	Age Baseline IMT Sonographer Height, weight, BMI Lipids Glucose Fibrinogen Smoking, Alcohol Physical activity Annual income Psychosocial job factors Work time	Men who worked weekend shifts experienced a faster progression of carotid atherosclerosis
Ramin et al., 2015	Cross-sectional, cohort of Nurses' Health Study II	54 724 women	2009	Ever night shift work	Never night shift work	CVD risk factors	Age SES	Ever night shift workers had increased odds of obesity, current smoking, and shorter sleep durations
Gu et al., 2015	Prospective cohort of Nurses' Health Study	74,862 women	1988 to 2010	Lifetime rotating night shift work (defined as ≥ 3 nights/month)	Women who never worked night shifts	All-cause mortality and deaths due to CVD	Age, SES Smoking, Alcohol BMI Physical activity Multivitamin use Menopausal status PM hormone use Healthy eating score Sleep duration 6-8h Hypertension Type 2 diabetes Hypercholesterolemia	All-cause and CVD mortality were increased among women with ≥ 5 years of rotating night shift work

BMI body mass index, BP blood pressure, CHD coronary heart disease, CRP C-reactive protein, CVD cardiovascular disease, HbA1c glycated haemoglobin, hsCRP high sensitivity C-reactive protein, IHD ischemic heart disease, IMT intima-media thickness, LPA leisure physical activity, MI myocardial infarction, PM post menopause, SES socioeconomic status, SW shift work, WC waist circumference.

Table 3. Reviews on the association of shift work with cardiovascular risk and risk factors.

Reference	Type of review	Number of articles included	Shift work definition/schedules and control group	Source of exposure information	Outcomes	Results
Frost et al., 2009	Systematic search for peer-reviewed epidemiological studies on the risk of ischemic heart disease in relation to night or shift work published until the end of March 2008 Medline	16 (3 included female shift workers) from 916 articles	SW: non-day work Control group: day worker, never worked in shifts	Self-reported questionnaires, company records, pay codes, registers	Fatal or non-fatal coronary disease, other cardiovascular diseases	Limited evidence of a causal association between shift work and IHD
Wang X-S. et al., 2011	Secondary review of the literature on shift work and chronic disease, from existing systematic reviews and original articles published prior to 31 December 2009 PubMed	4 systematic or critical reviews on CVD, 4 cohort, cross-sectional, and case-control studies on CVD (IHD, MI, ischemic stroke), 8 cohort or cross-sectional studies on MetS, 6 cohort or cross-sectional studies on DM	SW: any work schedule involving unusual or irregular working hours as opposed to a normal daytime work schedule	Not specified	Coronary artery disease, myocardial infarction, ischemic stroke, MetS (NCEP-ATPIII and IDF definitions), Diabetes, (fS-glucose ≥7.0, treatment for DM, DM mortality)	Epidemiological evidence graded according to the modified RCGP system was for the association between shift work and: -CVD: moderate -MetS: moderate -DM: limited

Reference	Type of review	Number of articles included	Shift work definition/schedules and control group	Source of exposure information	Outcomes	Results
Esquirol Y. et al., 2011	Systematic search of original articles published between January 2000 to December 2010 on the relationship between cardiovascular risk factors and shift work PubMed, Cochrane library and Embase	74 from 215 articles	different types of work schedules studied in the articles	Not specified	Blood pressure, blood lipids, MetS, BMI, diabetes parameters	Potential association between shift work and: -hypertension -triglycerides -MetS Possible association with -BMI No clear association with: -cholesterol -DM parameters
Vyas et al., 2012	Review and meta-analysis of the association between shift work and major vascular events Systematic search until 1 January 2012 Medline including PreMedline, Embase, BIOSIS Previews, Cochrane CENTRAL, Conference Proceedings Citation Index-Science, Google Scholar, ProQuest Dissertation Abstracts, Scopus, and Science Citation Index Expanded	35 (34 databases) from 12 350 articles	SW: evening, night, rotating, mixed, and irregular or unspecified shift schedule Control group: non-shift day workers (30) or general population (4)	From original study methodological descriptions	Primary outcomes: myocardial infarction, ischaemic stroke, any coronary event Secondary outcomes: heart failure, haemorrhagic stroke, mortality (total, CVD, coronary, cerebrovascular and all cardiovascular events)	Shift work associated with: -myocardial infarction -ischaemic stroke -coronary events Night shifts associated with: -coronary events

BMI body mass index, CVD cardiovascular disease, DM diabetes mellitus, HDL high density lipoprotein, IHD ischemic heart disease, IDF International Diabetes Federation, LDL low density lipoprotein, MetS metabolic syndrome, MI myocardial infarction, NCEP National Cholesterol Education Program Expert Panel, RCGP Royal College of General Practitioners 3-star system for the assessment of the strength of evidence, SW shift work, WC waist circumference, WHR waist to hip ratio.

Original studies

Karlsson et al. linked the 50 years' retrospective data from a cohort of industrial shift and day workers to the National Cause of Death Register. The results demonstrated an increased mortality from CHD for shift workers with the longest exposure time (>30 years). A trend of higher mortality due to ischemic stroke among shift workers was based on only four cases. There was no increase in total mortality among shift workers (Karlsson et al. 2005).

Fujino et al. studied the mortality risk of IHD among male shift workers. During the 233,869 person-years of follow-up, 304 deaths were attributed to circulatory system diseases and 86 to IHD. Compared with the day workers, the rotating shift workers had a significantly higher risk of death due to IHD. Fixed-night work was not associated with IHD. Subjects with coronary risk factors, such as hypertension, overweight, habitual alcohol consumption, and smoking, were highly susceptible to the effects of rotating shift work on the risk of death due to IHD, although the interaction effects were not statistically significant (Fujino et al. 2006).

Puttonen et al. examined the relationship between shift work and subclinical atherosclerosis in 1,543 young adults. Carotid atherosclerosis was assessed by measuring the thickness of the common carotid artery intima-media complex and carotid plaque with ultrasound. In the age-adjusted models, shift work was associated with a thicker mean intima–media, higher maximum values of intima–media, and a 2.2-fold odds for carotid plaque in men. The results suggested that shift work accelerates the atherosclerotic process and that the effects of shift work on subclinical atherosclerosis are observable in men already before the age of 40 (Puttonen et al. 2009).

Thomas and Power studied the associations between exposure to shift work and risk factors for cardiovascular disease and whether the associations were explained by socio-economic circumstances, occupational factors or health behaviours. Adverse levels of several CVD risk factors were found in association with increasing participation in shift work. Separate analyses of shift work types showed associations primarily for night/morning working rather than evening/weekend working. The relationships were explained by socio-economic, other occupational factors and health behaviours for most CVD risk factors examined (Thomas and Power 2010).

Wang et al. investigated the relationship between different work schedules and progression of carotid atherosclerosis in a prospective male cohort. The associations of baseline work schedules with the 11-year progression of ultrasonographically assessed carotid intima-media thickness, and their variation by pre-existing CVD. Compared to standard daytime work, weekend shifts induced a faster progression of carotid atherosclerosis and men with pre-existing CVD were especially vulnerable to the atherogenic effects of weekend shifts (A. Wang et al. 2015).

Ramin et al. examined the association between night shift work history and age when night shift work was performed with cancer and cardiovascular disease risk factors among women. The work schedules for each specific age range (20–25 years, 26–35 years, 36–45 years and 46+ years) were queried and categorized into day/evening, night, and early morning work. Ever night shift workers had increased odds for e.g. obesity, current smoking, and shorter sleep durations compared to never night shift workers. Night shift work before the age of 25 was associated with fewer risk factors compared to night shift work at older ages. The conclusion was that night shift work may contribute to an adverse chronic disease risk profile (Ramin et al. 2015).

Gu et al. examined associations between rotating night shift work and all-cause, CVD, and cancer mortality in a prospective female cohort study. Rotating night shift work information was collected once in 1988. Women working rotating night shifts for 5 years or more had a modest increase in all cause and CVD mortality (Gu et al. 2015).

Reviews

Frost et al. evaluated the epidemiologic evidence for a causal relation between shift work and ischemic heart disease (IHD) from original prospective studies. Point estimates of relative risks of IHD incidence and mortality ranged between 0.64 and 2.0. Two mortality data studies with a few cases reported an increase in risk, six mortality studies reported relative risks around unity. Six of the seven studies combining incidence data of non-fatal and fatal cases, reported relative risk slightly above unity, the associations were statistically significant in two studies. Thus the evidence of a causal association between shift work and IHD was deduced to be limited (Frost et al. 2009).

Wang et al. explored the epidemiologic evidence for an association between shift work and chronic diseases from systematic and critical reviews and other published data. The review provided suggestive but inconclusive evidence for a significant association between CVD and shift work, including night and rotating shift work. The more recently published data added some support for an adverse association. The authors graded the epidemiologic evidence for the association between shift work and CVD as moderate. One of the limitations of the published data was inadequate characterization of shift work exposure (X. S. Wang et al. 2011).

The aim of Esquirol et al. was to update the knowledge about shift work and cardiovascular risk in the review of Boggild and Knutsson (Boggild and Knutsson 1999), who noted a 40% higher relative risk of CVD among shift workers compared to day workers, for both genders. The included original articles dealing with the link between cardiovascular risk factors and shift work tended to document an impact of shift work on blood pressure, lipid profile (triglyceride levels), metabolic syndrome, and possibly on body mass index. The authors found it difficult to compare the studies because of the use of several definitions of shift work (Esquirol et al. 2011).

The objective of the systematic review and meta-analysis of Vyas et al. was to synthesize an association between shift work and major vascular events. In pooled random effects analyses, shift work status was associated with an increased risk of myocardial infarction and ischemic stroke. Coronary events were also increased, albeit with significant heterogeneity across studies. In pooled subgroup analyses, all types of shift work were associated with an increased risk of coronary events, with the exception of evening shift work. The highest point estimate was noted for night shifts. Shift work was not associated with increased rates of mortality, whether they were vascular cause specific or overall. Apart from the heterogeneity of the reviewed studies, the conclusion of the authors was that shift work is associated with myocardial infarction, coronary events, and ischemic stroke (Vyas et al. 2012).

In summary, original studies have demonstrated an increased mortality due to CVD as the number of shift years increase, in women even 5 years of rotating night shift work increased the risk. Night shift work probably contributes to an adverse chronic disease risk profile in women. Subjects with coronary risk factors were found to be susceptible to the effects of rotating shift work, exposing them further to the risk of death mediated through ischemic heart disease. Shift work may trigger the effects of other CVD risk factors, and it is probable that shift work accelerates the atherosclerotic process, as subclinical atherosclerosis has been observed in shift working men already before the age of 40. Weekend shifts may be hazardous, too, especially among middle-aged men with pre-existing CVD.
The reviews and meta-analyses suggest limited or moderate evidence for an association between shift work and cardiovascular risk. However, heterogeneity across the reviewed studies, several definitions of shift work, and inadequate characterization of shift work exposure detract from the certainty of the conclusions.

2.3.2 Shift work and type 2 diabetes

Pathways linking shift work to diabetes have been speculated by researchers. Circadian misalignment has been shown to disturb the glucose-insulin regulating system in experimental studies (Morris et al. 2015; Scheer et al. 2009). Another pathway could be sleep problems and sleep deprivation, which are common among shift workers (Ayas, White, Al-Delaimy, et al. 2003; Harma 2006; Zimberg et al. 2012). Stress is also a potential mechanism that could explain the increased risk of diabetes among shift workers (Eriksson et al. 2013; Harma, Kompier, et al. 2006). In addition, the increased risk of diabetes in shift work is supposed to mediate itself through body weight (Pan et al. 2011; Poulsen et al. 2014).

Recent research evaluating the association of shift work and type 2 diabetes are compiled in Tables 4 and 5.

Table 4. Original studies on the association of shift work and type 2 diabetes risk.

Reference	Study design	Participants	Time period	Shift work definition	Control croup	Outcomes	Adjusted covariates	Results
Morikawa et al., 2005	Cohort of Japanese factory workers	2,860 men 228 2-shift workers, 492 3-shift workers	1993 to 2001	3-SW (counter clockwise continuous or discontinuous), 2-SW (day- or evening shifts)	1099 fixed daytime blue-collar workers and 1041 white-collar day workers	HbA1c ≥6.1 or DM diagnosed by a hospital physician	Age, BMI, family history, smoking, drinking, LTPA	A trend towards a higher risk of DM among shift workers and a significantly increased risk of DM among 2-shift workers
Karlsson et al., 2005	Retrospective study from a Swedish cohort in the pulp and paper industry, linked to the National Cause of Death Register	2,354	1952 to 2001	Mainly rotating three-shift schedule	3,088 day workers	Total mortality Mortality from coronary heart disease, stroke, and diabetes		A trend towards increasing mortality due to diabetes with an increasing number of shift years
Suwazono et al., 2009	Prospective cohort study in a Japanese steel company	7,104 men 2,885 shift workers	1991 to 2005	Determined from the payment ledger in May of each year. Clockwise rotation 3-SW	4,219 day workers	HbA1c ≥ 6.0%, DM (diagnosed by a hospital physician , Rx)	Age, BMI, drinking, smoking, exercise habits, blood pressure, total cholesterol, creatinine, ALT, GGT,UA	Alternating shift work is an independent risk factor for the development of DM

Reference	Study design	Participants	Time period	Shift work definition	Control croup	Outcomes	Adjusted covariates	Results
Pan et al., 2011	Prospective cohorts of studies I and II of the Nurses' Health Study	69,269 women	1988 to 2005	Self-reported rotating night shifts ($\geq$ 3 nights/month)	Women who reported no SW	Self-reported T2D	Weight, smoking, drinking habits, physical activity, MP and Rx, family history of DM, diet, sleep, social status	Rotating night shift work was associated with a modestly increased risk for T2D, partly mediated through body weight
Poulsen et al., 2014	Prospective observational cohort of health care workers, linked to the Danish National Diabetes Register	7,305 women	2005 to 2012	Working hours were self-reported	Work entirely/partly during daytime	Register information of DM diagnosis, diabetes-related chiropody care, blood glucose measurements or Rx	Self-assessed LTPA, physical capacity, smoking, BMI	Shift work (evening/night) associated with an increased risk for diabetes
Vetter et al., 2015	Prospective cohort of Nurses' Health study II	64,615 women	2005 to 2011	Shift work exposure assessed regularly since 1989 by questionnaire	Intermediate chronotype	Newly developed T2D	Weight, smoking, drinking habits, physical activity, MP and Rx, family history of DM, diet, sleep, depressive symptoms, social status	DM risk increased with increasing duration of shift work exposure in early chronotypes, whereas late types had the highest risk when working daytime schedules

ALT alanine aminotransferase, BMI body mass index, DM diabetes mellitus, DW Day work, GGT γ-glutamyl transpeptidase, HbA1c glycated haemoglobin, LTPA leisure time physical activity, MP menopause, SW shift work, Rx pharmacologic treatment, T2D type 2 diabetes, UA uric acid.

Table 5. Reviews on the association of shift work and type 2 diabetes risk.

Reference	Type of review	Number of articles included	Shift work definition/schedules and control group	Source of exposure information	Outcomes	Results
Wang et al., 2011	Systematic and critical reviews and original studies published prior 2010	From 550 references 6 studies were included	Any work schedule involving unusual or irregular working hours as opposed to a normal daytime work	From original study methodological descriptions	DM, T2D, FS-glucose $\geq$7 mmol/l, Rx, mortality due to DM	Limited evidence (RCGP*) for the association between SW and DM
Knutsson and Kempe, 2014	Systematic review of epidemiologic cohort studies published until 1 Nov 2012	From 181 references 5 studies were included	Rotating SW/DW, rotating 3-shift, rotating night-shift, 2-shift, 3-shift, DW	From original study methodological descriptions	T2D, DM, HbA1c $\geq$6.1, OGTT, mortality due to DM	Moderate evidence (RCGP**) on an association between SW and T2D
Gan et al., 2015	Meta-analysis of observational studies to April 2014	28 references from 12 studies, 226,650 participants	SW schedules were classified according to the original study methodological description as rotating, irregular and unspecified, night, mixed and evening. Control group individuals who had never been exposed to shift work	From original study methodological descriptions	DM	SW work was associated with an increased risk of DM compared to DW

DM diabetes mellitus, DW daytime work, FS fasting serum, HbA1c glycated haemoglobin, OGTT oral glucose tolerance test, RCGP Royal College of General Practitioners three-star system for the assessment of the strength of evidence, Rx pharmacologic treatment, SW shift work, T2D type 2 diabetes.

Original studies

Morikawa et al. followed a cohort of Japanese male factory workers for 8 years. Compared to the fixed daytime workers there was a trend towards a higher risk of diabetes mellitus among shift workers overall. When the white-collar workers were used as a reference group, a significantly increased risk of diabetes mellitus was found for the 2-shift workers, but not for the 3-shift workers, nor the fixed daytime blue-collar workers. The authors concluded that the study suggested shift work was a risk factor for diabetes mellitus and that the risk is different for different shift schedules (Morikawa et al. 2005).

The abovementioned Swedish retrospective cohort study of Karlsson et al. revealed that diabetes was more common as the number of shift years of exposure increased. There was also a trend towards increasing mortality due to diabetes with an increasing number of shift years (Karlsson et al. 2005).

Suwazono et al. conducted a 14 year prospective Japanese male cohort study to assess the effect of shift work on glucose metabolism. Shift work was significantly associated with the various HbA1c endpoints. The authors concluded that alternating shift work is a consistent risk factor for impaired glucose metabolism among men (Suwazono et al. 2009).

Pan et al. explored two prospective cohorts in the Nurses' Health study and concluded that an extended period of rotating night shift work was associated with a modestly increased risk for type 2 diabetes in women. The risk appeared to be partly mediated through body weight (Pan et al. 2011).

To study lifestyle and working conditions with the risk of developing diabetes Poulsen et al. conducted a study by linking a cohort of female health care workers with the diabetes register. During a 7-year follow up, 3.5% of the participants developed diabetes that was associated with obesity, overweight, and age. In the occupational setting, obesity was associated with shift work (Poulsen et al. 2014).

Vetter et al. examined whether a mismatch between chronotype (i.e., preferred sleep timing) and work schedule is associated with T2D risk. In the Nurses' Health Study II, chronotype was queried with a single question on diurnal preference in 2009. The results showed increasing diabetes risk with increasing duration of shift work exposure in early chronotypes, whereas late types had the highest diabetes risk when working daytime schedules (Vetter et al. 2015).

Reviews

Wang et al. explored the epidemiological evidence for an association between shift work and chronic diseases. Based on the fact that there have been several studies but only one which reported a statistically significant elevated risk of diabetes among shift workers, the authors found the epidemiologic evidence to be limited for an association between shift work and diabetes (X. S. Wang et al. 2011).

Knutsson and Kempe studied the potential association between shift work and type 2 diabetes. Five articles of epidemiological cohort studies with relevant exposure and outcome information as well as adequate participants were included in the review. In spite of the low number of studies and low methodological quality in some studies, the authors concluded that there is moderate evidence for an association between shift work and type 2 diabetes (Knutsson and Kempe 2014).

In the meta-analysis of Gan et al. all shift work schedules with the exception of mixed shifts and evening shifts were associated with an increased risk of diabetes compared to normal daytime work. The risk was significantly higher among men than women and in the rotating shift work group. In his letter, Rahman Shiri pointed out some potential biases in the results relating to gender difference i.e. study size, selection and exposure (Shiri 2014). The authors, however, responded that these defects did not alter the main results and conclusions of their study (Gan et al. 2015).

In summary, original studies suggest an increased risk of diabetes among blue-collar men in 2-shift work and alternating shift work. Among men, diabetes seems to be more common as the number of shift years of exposure increases and there is also a trend towards an increased risk of death due to diabetes along with increasing years of shift work. Among women, rotating night shift work has been associated with the risk of diabetes, partly mediating through body weight. Chronotype probably modifies some results.
From the review studies, the evidence for a causal association between shift work and type 2 diabetes is inconclusive. However, the most recent meta-analysis supported the association, which was higher among men and stronger for rotating shift work.

2.3.3 Shift work and metabolic syndrome

By disturbing sleep and our natural biological bodily rhythms as well as increasing psychosocial stress, shift work predisposes individuals to physiological disturbances related to metabolic syndrome.

Original studies

In a population-based prospective study, a total of 1,529 male employees were followed for 6.6 years with respect to the onset of the MetS and its separate components. The MetS (modified IDF criteria) incidence rate among 309 shift workers was increased in comparison with day workers. The risk for the development of MetS gradually increased with accumulated years of shift work. Rotating shift work had an impact on each of the individual components of MetS, as well (De Bacquer et al. 2009).

A retrospective cohort study on the development of metabolic syndrome was conducted by Lin et al. utilizing health examination records of 387 female employees without metabolic syndrome at baseline. The female workers with persistent day-night rotating shift-work exposure had a 3.5-fold greater risk of developing MetS (modified NCEP-ATPIII criteria) compared with those having a persistent day job (Y. C. Lin et al. 2009).

Pietroiusti et al. studied the development of metabolic syndrome among 402 male and female nurses performing night shifts and 336 daytime workers. During a 4-year follow-up, the development of MetS was significantly higher in night-shift healthcare workers than in daytime healthcare workers. The authors concluded that the risk of developing NCEP-ATPIII defined MetS is strongly associated with night-shift work in nurses (Pietroiusti et al. 2010).

Kawada et al. conducted a 3-year follow-up study of an occupational cohort of 1,677 Japanese male employees to clarify the effect of the type of shift work on the risk of development of NCEP-ATPIII defined MetS. The results suggested that 2-shift work, but not 3-shift work, was a risk factor for the development of metabolic syndrome (Kawada and Otsuka 2014).

In a recent Chinese cohort of retired workers (n=26,382), NCEP-ATPIII defined metabolic syndrome associated with shift work exposure of 11 years or more. Among female workers, every 10-year increase in shift work exposure was associated with a 10% elevated OR of MetS (Guo et al. 2015).

Reviews

Canuto et al. included ten original articles in their review to examine the association between shift work and metabolic syndrome. When the demographic, socioeconomic and behavioural variables as confounders were taken into account, there was insufficient evidence for any association between shift work and prevalent MetS (Canuto et al. 2013).

Wang et al. studied the association between the risk of MetS and night shift work and summarized all the published epidemiological studies with special reference to the dose–response relationship. The authors concluded that the results suggested that night shift work is significantly associated with the risk of MetS with a positive dose–response relationship (F. Wang et al. 2014).

In summary, retrospective and prospective large cohort studies as well as longitudinal smaller studies suggest that among both genders metabolic syndrome associates with shift work and there is a dose-response trend.
The reviews show limited evidence for an association between shift work and MetS, apart from night shift work.

2.3.4 Shift work induced sleep problems and related health effects

The most common health-related effects of shift work are disturbed and shortened sleep. Shift work affects sleep causing desynchronization of the sleep–wake cycle from the normal circadian rhythm when working hours overlap the natural sleep period (circadian disruption). In addition, shift work is often accompanied by reduced sleeping hours (sleep loss) (Akerstedt 2003; Akerstedt and Wright 2009). The subjective ratings have shown a significant difference between morning, afternoon and night shifts for sleep length, ease of falling asleep, ease of awakening, too early awakening, and being well rested. Sleep after a night shift and before a morning shift is reduced by 2–4 hours (Akerstedt et al. 1991; Torsvall et al. 1989). After a night shift, acute symptoms are associated with premature awakening and somnolence during working hours that continues into successive days off (Akerstedt 2003). Apart from reduced length, sleep before the morning shift seems to be associated with difficulties in getting to sleep and in awakening, non-spontaneous awakening and a decreased feeling of being well rested. The afternoon shift is the least afflicted of the three shifts (Akerstedt et al. 1991).

Circadian disruption is the central mechanism connecting shift work to ill health (Akerstedt 2003), it causes shift work sleep disorder and a disruption of the circadian rhythms of many nutritional, cardiovascular, immunological, and metabolic functions. Insufficient or poor sleep, related to insufficient recovery, can be a pathway from shift work to cardiovascular illness (Harma 2006). Subjects exposed to sleep restriction have shown an increased activation of the stress response systems (Mullington et al. 2010; Patel et al. 2009; Spiegel et al. 1999; van Leeuwen et al. 2009). The plausible physiological and biological mechanisms of circadian disruption and shortened or disturbed sleep in shift work have been related to the activation of the autonomic nervous system, inflammation, changes in lipid and glucose metabolism, and related changes in the risk for metabolic syndrome, type 2 diabetes, and atherosclerosis (Zimberg et al. 2012).

Obesity

Sleep deficiency and chronic stress related to circadian disruption, can affect the body's endogenous signals and thereby contribute to failures in the homeostatic control of food intake. Short sleep duration is associated with decreased leptin levels, increased ghrelin levels, and increased hunger and appetite (Lowden et al. 2010). Many systematic reviews and meta-analyses have suggested that short sleep duration may be a novel and independent risk factor for weight gain and obesity (Bayon et al. 2014; Cappuccio et al. 2008; Patel and Hu 2008; Van Cauter and Knutson 2008). Magee and Hale performed a systematic literature search to examine the relationship between sleep duration and subsequent weight gain. Twenty longitudinal studies published from 2004 to October 2010 revealed that while shorter sleep duration consistently predicted subsequent weight gain in children, the relationship was not clear in adults probably due to the limitations of the studies (Magee and Hale 2012). However, several cross-sectional studies have reported a U-shaped association between sleep duration and weight in adults with the lowest BMI associated with a sleep duration of 7–8 hours (Chaput et al. 2007; Gangwisch et al. 2005; Taheri et al. 2004). In an experimental sleep restriction study among 225 healthy adults, sleep-restricted subjects gained more weight than control subjects, and men gained more weight than women. Sleep-restricted subjects also consumed extra calories during days with a delayed bedtime compared with control subjects (Spaeth et al. 2013). St-Onge examined the literature focusing on adult clinical studies to determine if alterations in sleep duration lead to changes in the energy balance equation. The studies showed a clear pattern of increased food intake during periods of restricted sleep (St-Onge 2013). Antunes et al. summarized the chronobiologic aspects of shift work and obesity in their literature review. Their conclusion was that there is considerable epidemiologic evidence that shift work is associated with an increased risk for obesity, diabetes and CVD, perhaps as a result of physiological maladaptation to chronically sleeping and eating at abnormal circadian times (Antunes et al. 2010).

Glucose metabolism

Sleep deficit and sleep disturbances, typical in shift work, could contribute to the development of insulin resistance and type 2 diabetes either directly by having a deleterious effect on components of glucose regulation or indirectly via a dysregulation of appetite (Spiegel et al. 2005). Daily patterns of energy expenditure, hormones, and lipids involved in energy metabolism (e.g., leptin, ghrelin, glucose, insulin, glucocorticoids, catecholamines, fatty acids, triglycerides) are regulated by sleep and circadian rhythms. Sleep deficiencies and circadian disruption associated with metabolic dysregulation may contribute to weight gain, obesity, and type 2 diabetes potentially by altering the timing and amount of food intake, disrupting energy balance, impairing glucose tolerance, and insulin sensitivity (Depner et al. 2014; St-Onge 2013; Van Cauter et al. 2007).

In an experimental study of 11 healthy young men glucose tolerance was lower, evening cortisol concentrations raised, and the activity of the sympathetic nervous system increased in sleep-debt conditions. The authors stated that sleep debt has a harmful impact on carbohydrate metabolism and endocrine function, similar to those seen in normal ageing (Spiegel et al. 1999).

A recent review (Briancon-Marjollet et al. 2015) provides endocrine and molecular explanations for the associations between short sleep and circadian rhythm disruption with the pathogenesis of T2D. The authors conclude that the most likely mediators are the activation of hypothalamic-pituitary-adrenal axis with increased circulating cortisol levels, misalignment between the central and peripheral pacemakers, enhanced lipolysis and modified adipokine release in adipose tissue, sympathetic nervous system activation, and the induction of a whole-body proinflammatory state. Disruption of circadian rhythms (e.g. in shift work and sleep loss) may also contribute to β-cell failure, essential for the development of type 2 diabetes (Rakshit et al. 2014).

Inflammation

It has been suggested that sleep loss itself may contribute to inflammation and, if chronic, to cardiovascular risk. Sleep loss may be one of the ways that inflammatory processes are activated and contribute to the association of sleep complaints and short sleep duration with the cardiovascular morbidity observed in epidemiologic surveys. In experimental studies both acute total and short-term partial sleep deprivation have resulted in elevated high-sensitivity CRP concentrations (Meier-Ewert et al. 2004). Sleep restriction has increased lymphocyte activation and the production of pro-inflammatory cytokines accompanied by increased heart rate and serum CRP, which are two important risk factors for cardiovascular diseases (van Leeuwen et al. 2009). An experimental study suggested that the circadian misalignment that occurs in shift work may increase diabetes risk and inflammation probably independently of sleep loss. In spite of an identical amount of daily sleep, the reduction in insulin sensitivity and the increase in inflammation doubled among participants exposed to experimental circadian misalignment, compared with those who maintained regular nocturnal bedtimes (Leproult et al. 2014).

Autonomic nervous system response

Heart rate and heart rate variability reflect cardiac sympathic/parasympathic balance. Epidemiological studies have confirmed an elevated resting heart rate as an independent predictor of cardiovascular mortality (Caetano and Delgado Alves 2015), and reduced heart rate variability has long been associated with risk for cardiac events (Tsuji et al. 1996). The autonomic nervous system is modulated by sleep and wakefulness. In experimental studies prolonged wakefulness reduced heart rate variability among healthy young men (Glos et al. 2014) and after multiple nights of short sleep heart rate increased (van Leeuwen et al. 2009), both indicating autonomic stress due to sleep deprivation. In an experimental study, heart rate variability parameters differed significantly between shift and non-shift workers despite the circadian phase. The authors concluded that this probably reflects higher sympathetic and/or lower parasympathetic activity among the shift workers, which may contribute to increased cardiovascular risk (Wehrens et al. 2012).

Ageing

Sleep quality changes across the human life span (Ohayon et al. 2004). Poor sleep quality is a temporary consequence of shift work for many, whereas for others it is a cause of shift work intolerance (Tucker et al. 2011). Epidemiologic studies indicate that 40–70% of the elderly population suffer from chronic sleep disturbances (Van Someren 2000) e.g. primary sleep disorders, insomnia, and circadian rhythm disturbance (Roepke and Ancoli-Israel 2010). Sleep complaints among shift workers increase with age and sleep becomes less consolidated. Tolerance to shift work is affected, for instance, by age and chronotype (morningness) (Saksvik et al. 2011). Ageing is associated with increased “morningness” and seems to increase sleepiness along with consecutive night shifts due to an insufficient circadian adjustment (Harma et al. 1994). Based on questionnaires the critical age for developing disturbances in sleep and wakefulness is on average 40–50 years (Harma et al. 1992; Koller 1983). In a cohort study of 3,236 wage earners and retired workers, age resulted in a continuously increasing frequency of sleep disturbances, which peaked at 52 years and then decreased, suggesting a ‘retirement effect’. Current and past shift workers reported more problems with falling asleep and early awakening than subjects who had never worked in shifts (Marquie and Foret 1999). In their systematic review, Blok and Looze deduced when compared to younger workers, older workers have more sleep problems with night shifts, while the opposite is true for morning shifts. The review revealed limited evidence concerning shift work tolerance in older workers. In view of some interactions between age, shift type and shift system, the authors concluded that age-specific aspects should be considered in shift work planning (Blok and de Looze 2011).

2.3.5 Shift work and lifestyle habits

Shift work may alter employees’ lifestyles in many ways. Shift workers’ health habits are irregular compared to those of day workers. The review of Boggild and Knutsson revealed that shift workers smoked more than day-workers. They were already smokers when they began to do shift work (Boggild and Knutsson 1999). On the other hand, shift work or irregular working hours may predispose employees to unhealthy lifestyle habits (Johansson et al. 1991; Nea et al. 2015). Shift working also includes elements of work stress (Puttonen et al. 2010), and work-related stress, in turn, has been associated with unhealthy living habits especially smoking, alcohol consumption, physical inactivity, and being overweight (Heikkila et al. 2013; Nyberg et al. 2013; Siegrist and Rodel 2006). The evidence for a relationship between shift work and physical inactivity is inconclusive. Recreational inactivity has been associated with current night shift work when compared to never night shift workers among men (Peplonska et al. 2014). However, some studies have found shift workers' lifestyle even less sedentary when compared to daytime workers (Loprinzi 2015; Ma et al. 2011).

Factors that affect the metabolism may be linked to quality of diet and irregular timing of eating. The review of Lowden et al. evaluated the results of shift workers' dietary intake studies and discovered that total energy intake does not vary between day and shift workers. However, shift working affects the amount eaten, the quality of the dietary intake, and energy distribution over the course of the day. In addition to the endogenous factors underlying failed homeostatic control of food intake, there are a range of possible exogenous e.g. social contributors (Lowden et al. 2010).

Shift work can change food timing and healthy dietary habits can be difficult to maintain, especially if the facilities for eating outside the normal working hours are not well organized and healthy food choices are not available. Food and nutrient intake differences between working time groups were studied by Hemiö et al. using sub-data from the health check-up study of this dissertation. Shift work and working environment were associated with dietary habits, and this association was not explained by other characteristics such as workers' educational levels. Shift working men consumed less vegetables and fruits than male day and in-flight workers. In women, higher energy intake from saturated fats was found among shift workers and from fat and saturated fat among older shift workers, compared to day workers (Hemio et al. 2015).

2.3.6 Methodologic issues in shift work research

Selection bias, confounders and mediators, as well as exposure assessment are methodological problems in shift work research. Working conditions and exposure may differ between shift and day workers in terms of risk factors for CVD (e.g. cardiotoxic chemicals, environmental smoke, sedentary surveillance work). Shift workers often differ from day workers also in socioeconomic status, educational level, and lifestyle habits, all of which are associated with the risk of CVD. Age is a major risk factor for CVD, and shift workers are in general younger than day workers, as shift workers change to day work for different reasons (e.g. sleep, health, "reward").

Selection

Selection into and out of shift work is an important methodological problem in shift work research and difficult to take into account as the reasons for selection are not known. Compared to day workers those who self-select working in shifts probably have different sleeping habits and other individual factors which may mediate CVD risk. In the abovementioned cohort study of Marquié and Foret, sleeping problems peaked at the age of 52 years and then decreased. The authors deduced that a selection process excludes workers who are no longer able to cope with the demands of shift work (Marquie and Foret 1999).

Kivimäki et al. followed a cohort of female nurses (5,038 shift workers, 1,999 day workers) for 2 to 4 years. Prevalent CVD, elevated blood pressure, high cholesterol concentration, obesity, and diabetes at baseline were equally predictive of leaving the organization among both the shift and day workers. The authors concluded that health-related selection out of shift work is an unlikely source of major bias in research on shift work and CVD (Kivimaki et al. 2006).

Yong et al. studied if the differences in health behaviour and health outcomes of shift and day workers can be caused by primary selection. The findings among 4,754 male trainees who had finished their professional training and started their careers in a chemical company (28% in rotating shift work and the rest in day work) did not support a primary selection in favour of shift workers. An impact of shift work on the risk profile of cardiovascular diseases was not indicated in the three-year observation period (Yong et al. 2015).

Nabe-Nielsen et al. examined differences between future shift workers and future day workers as regards cardiovascular risk factors. Compared with future day workers, fixed evening or fixed night workers already smoked more before they began shift work. Being an ex-smoker was significantly associated with 2- or 3-shift work including night work. The authors concluded that smoking status should not solely be treated as a mediator between some variants of shift work schedules and cardiovascular diseases but should also be considered to be a confounder (Nabe-Nielsen et al. 2008).

Exposure assessment

A limitation of epidemiological shift work studies are their poor exposure assessments. The International Agency for Research on Cancer convened a workshop in April 2009 to consider how 'shift work' should be assessed. The major domains of a shift and shift schedule that are important to capture are: (1) shift system (start time of shift, number of hours per day, rotating or permanent, speed and direction of a rotating system, regular or irregular); (2) years on a particular non-day shift schedule and cumulative exposure to the shift system over the subject's working life; (3) shift intensity (time off between successive work days on the shift schedule). These domains are based in part on the biological considerations that adaptation can occur more quickly after a phase delay than a phase advance (Stevens et al. 2011).

However, questionnaire or interview-based data on working hours provide only crude information which makes exposure measurements also an important source of bias for systematic reviews. Objective, register-based exposure assessment methods to clarify the effects of shift work on chronic diseases are needed. A method to retrieve standard payroll data for working hours from an employer's electronic records has recently been developed and validated (Harma et al. 2015).

2.4 Prevention of cardiovascular risk

CVD prevention is defined as a co-ordinated set of actions aimed at eradicating, eliminating, or minimizing the impact of cardiovascular diseases and their related disability. The epidemiologist Geoffrey Rose decades ago proposed two approaches towards the prevention of CVD; the population strategy and the high-risk strategy. The population strategy aims at reducing the CVD incidence at the population level through lifestyle and environmental changes targeted at the population at large. In the high-risk approach, preventive measures are aimed at reducing risk factor levels in those at the highest risk (Rose 1981). The World Health Organization has stated that over three-quarters of all CVD mortality may be prevented by adequate changes in lifestyle. The 2012 guidelines from the Fifth Joint Task Force of the European Societies on Cardiovascular Disease Prevention in Clinical Practice give an update of the present knowledge in preventive cardiology for physicians and other health workers (Perk et al. 2012).

2.4.1 Concept of prevention

In the 1940s, Leavell and Clark coined the term 'primary prevention' and later expanded the levels to include secondary and tertiary prevention (Leavell and Clark 1965). The dictionary of epidemiology edited by John M. Last (Last 1995) describes prevention as 'promoting and preserving health, restoring health when it is impaired, and minimizing suffering and distress'. Primary prevention can be defined as the protection of health by personal and communitywide effects, e.g., preserving good nutritional status, physical fitness, and emotional well-being, immunizing against diseases, and making the environment safe. Secondary prevention can be defined as the measures available to individual and populations for the early detection and prompt and effective intervention to correct departures from good health. Tertiary prevention consists of the measures available to reduce or eliminate long-term impairments and disabilities, extending the concept of prevention into the field of rehabilitation.

Work place health programmes usually not only focus on disease prevention but also on health promotion (Fronstin 1996). Health promotion is a more comprehensive process of enabling people to increase control over, and to improve, their health to reach a state of complete physical, mental and social well-being ("First International Conference on Health Promotion, Ottawa, 21 November 1986"). Health promotion is not just the responsibility of the health sector, but goes beyond a healthy lifestyle to well-being. ‘To make the healthy choice the easy one’, is the famous slogan the Ottawa conference uses to call for health considerations to be taken into account in policy-making across sectors and society at large (Puska 2014).

Primary prevention addresses the root cause of a disease whereas secondary prevention aims to detect and treat a disease early on. Screening of risk factors (e.g. blood glucose) in a health check-up is a method of primary prevention, but also secondary prevention in detecting a latent existing disease (e.g. type 2 diabetes) prior to the appearance of symptoms. In this thesis, the methods of preventing cardiovascular disease and type 2 diabetes in occupational settings include screening for risk factors, lifestyle counselling, and recommendations for healthy working times and thus they mostly belong to the category of primary prevention.

2.4.2 Prevention of cardiovascular disease and type 2 diabetes

As cardiovascular diseases and type 2 diabetes share common risk factors including metabolic syndrome, initiatives to screen and prevent CVD and T2D support each other. The most common avoidable lifestyle risk factors obesity, a sedentary lifestyle and unhealthy diet predispose to type 2 diabetes (Hu et al. 2003; Lindstrom, Peltonen, et al. 2006; "World Health Organisation " 2003). Gradual weight gain during the adult years, especially abdominal obesity increases the risk of obesity-related metabolic disorders, type 2 diabetes and metabolic syndrome, both related to cardiovascular morbidity. Smoking is a strong independent risk factor for CVD but is also associated with increased risk for T2D (Barrett-Connor and Khaw 1989; Canoy et al. 2005; Willi et al. 2007) and thus lifestyle counselling to support quitting smoking is important in preventing both CVD and T2D. Circadian disruption and the duration and quality of sleep also affect metabolic health and are associated with the risk of cardiometabolic diseases (Harma 2006; Knutson et al. 2006).

2.4.2.1 Lifestyle counselling

Intensive lifestyle interventions in experimental settings reduce T2D among high risk individuals (Li et al. 2008; Lindstrom, Ilanne-Parikka, et al. 2006; Lindstrom et al. 2013; J. Tuomilehto et al. 2001; J. Tuomilehto et al. 2011). Even less intensive methods of counselling individuals at high risk for diabetes have been demonstrated to be feasible, though not as effective in real-life settings (Absetz et al. 2009; Laatikainen et al. 2007; Saaristo et al. 2010).

In clinical practice cognitive-behavioural methods are effective in supporting individuals in adopting a healthy lifestyle. Individualized counselling is the basis for evoking and gaining the patient's motivation and commitment. Health technology methods, telemedicine and e-health have been shown to be effective for type 2 diabetes patients in providing them with education and awareness of their well-being and assisting them in their weight management and blood glucose level control (Jalil et al. 2015). Moving forward in small, consecutive steps is one of the key points in changing long-term behaviour. Multimodal behavioural interventions are especially recommended for individuals at very high risk (Perk et al. 2012).

In the Finnish Diabetes Prevention Study, none of the high-risk individuals with impaired glucose tolerance developed diabetes during the initial trial period if they reached at least four of the five predefined lifestyle targets (weight loss >5%, intake of fat, 30% energy, intake of saturated fats, 10% energy, increase of dietary fiber to ≥15 g/1,000 kcal, and increase of physical activity to at least 4 h/week) (J. Tuomilehto et al. 2001). Beneficial lifestyle changes were maintained after the discontinuation of the intervention. During the 7-year follow-up, the incidences of T2D were 4.3 and 7.4 per 100 person-years in the intervention and control group, respectively, indicating a 43% reduction in relative risk (Lindstrom, Ilanne-Parikka, et al. 2006). After the 10-year follow-up, however, total mortality and cardiovascular morbidity did not differ significantly between the intervention and control groups, according to the authors probably due to insufficient statistical power to detect small differences between the groups (Uusitupa et al. 2009).

The review of Sanz et al. aimed to assess the effect of exercise on the prevention of type 2 diabetes in high-risk individuals. They found strong evidence that physical exercise can prevent or delay the progression of impaired glucose tolerance to type 2 diabetes. The authors concluded that physical exercise should be part of any therapeutic strategy to slow the development of type 2 diabetes in high-risk individuals. However, the need for strong coaching to make people change their lifestyles may be the main limitation for implementing prevention trials in the general population (Sanz et al. 2010).

Tuomilehto et al. state in their paper that the trials documented thus far have provided a good basis, but there is a lot to do to find the most effective methods for type 2 diabetes prevention in various societies and cultural settings. The most important issue, however, is to implement and evaluate community-based efforts aimed at preventing type 2 diabetes. However, this cannot be done without actual programmes implemented in real-life settings (J. Tuomilehto et al. 2011).

Based on the results of the DPS, a nationwide programme for the prevention of type 2 diabetes was launched in Finland as part of the Finnish National Diabetes Program (DEHKO 2000–2010). The implementation project of the programme, called FIN-D2D, was carried out during 2003–2008 in primary and occupational health care within five hospital districts, encompassing 1.5 million people (Saaristo et al. 2007). One of the goals of the programme was to raise awareness of diabetes and its risk factors in the whole population. The structured questionnaire mailed in 2004–2008 to a random population sample included questions on participants' sociodemographic background, medical history, health habits, and recent lifestyle changes as well as their awareness of the DEHKO programme. Data from the surveys (n=10,831) suggested that health promotion campaigns increase the population's awareness about the prevention of chronic diseases and as a result, especially men may be prompted to make beneficial lifestyle changes (Wikstrom et al. 2015).

In their review and meta-analysis of randomized clinical trials, Galani and Schneider evaluated lifestyle interventions in the prevention and treatment of obesity. A subgroup analysis was performed in overweight people with cardiovascular risk factors. Compared with standard care, lifestyle intervention significantly reduced weight, BMI, waist circumference, blood pressure, blood lipids and blood glucose among overweight and obese people and the favourable effects were maintained for up to three years (Galani and Schneider 2007).

The systematic review of Lin et al. revealed that intensive diet and physical activity behavioural counselling in persons with risk factors for cardiovascular disease resulted in consistent improvements across various important intermediate health outcomes (weight, BP, lipids, glucose, diabetes risk) up to 2 years (J. S. Lin et al. 2014).

In summary, intensive lifestyle interventions in experimental settings effectively reduce T2D among high risk individuals. Also, intensive interventions targeted at populations with an elevated risk for CVD have been profitable. Individualized counselling in small, consecutive steps using multimodal, cognitive-behavioural methods is recommended for individuals at high risk. Health technology methods may be helpful and effective in counselling. However, the need for strong coaching to make people change their lifestyles may be the main limitation to implementing prevention trials for the general population. Implementing and evaluating community-based efforts for prevention cannot be done without actual programmes in real-life settings.

2.4.3 Prevention of cardiovascular risk and type 2 diabetes in shift work

The paper of Giovanni Costa (Costa 2010) gives an overview of the problems to be tackled by occupational health care to protect shift workers' health and well-being. He states that appropriate interventions for the organization of shift schedules according to ergonomic criteria and careful health surveillance are important preventive measures that allow people to keep working without significant health impairment.

Mikko Härmä states in his review article (Harma 2006) that the most promising worktime-related means for decreasing the negative health effects of workhours would be to regulate overtime and excessive workhours, to increase individual worktime control, and to increase recovery by the introduction of sleep-promoting principles into shift rotation.

In their commentary on the study of Pan et al. (Pan et al. 2011) exploring the association between type 2 diabetes and rotating night shift work, Axelsson and Puttonen presented strategies to reduce health risks among shift workers. They stated that first of all, organizations should acknowledge that shift work is a metabolic risk factor and actively use strategies to improve shift-workers’ life-styles. The use of ergonomic working schedules should be adopted more widely and health screening and regular health check-ups for individuals who may be vulnerable to shift work or its health effects are needed. Also, shift-workers need to be educated to cope better with shift-work (eating, sleeping and exercising) and the use of countermeasures (for instance naps) should be widened (Axelsson and Puttonen 2012).

2.4.3.1 Shift schedule design

The arrangement of working hours has become a crucial factor in work organizations to prevent or reduce the health problems caused by shift work. There is no ideal shift system, and guides for shift work design have been published even by labour unions ("Unite guide to shift work and night work – a health and safety issue for Unite members" 2013). To design a tailor-made shift system, a compromise has to be found between the company’s goals, the workers’ wishes and relevant ergonomic recommendations.

In their review, Knauth and Hornberger present twenty ergonomic recommendations which may help to improve existing shift systems, involving the sequence of shifts, the duration, distribution, and position of working time, as well as the short-term deviations from the set shift system. Permanent night work, consecutive night shifts more than three, extension of shifts to 10 or 12+ hours, and very early morning shifts, for instance, are working situations which may result in sleep deficit and increase the risk of fatigue. On the other hand, adequate time off between shifts, forward rotation of shift schedules and the possibility for individual flexibility in working times may help cope with shift work. The authors suggest trying combinations of measures to reduce the psychological, social and health problems of shift workers (Knauth and Hornberger 2003).

Circadian adjustment to night work in rotating shift systems may not be desirable, and the choice of especially rapid forward-rotating shift systems seems to give the fastest recovery in relation to both sleep–wakefulness and the possibilities to utilize the days off after night shifts in social and family life. In irregular shift systems, the avoidance of quick returns and early morning and night shifts are related to longer night sleep and improved possibilities for daytime napping (Harma 2006).

In their review, Sallinen and Kecklund examined what level of research evidence is available to support that shift workers' sleep-wake disturbances can be minimized through ergonomic shift scheduling. The results of the observational studies, in which no changes to the shift system were made, showed that irrespective of the shift system, night and early-morning shifts, quick returns, very long shifts (>16 hours) and extremely long weekly working hours (>55 hours) are associated with short sleep and increased sleepiness. Intervention studies, mostly non-randomized and conducted in regular 3-shift systems, suggested that a change from slowly backward rotating shifts to rapidly forward-rotating shifts was advantageous for alertness and, to some degree, for sleep. The authors concluded that the level of research evidence for ergonomic recommendations on improving shift schedules is degraded by the lack of controlled intervention studies as well as the lack of observational studies comparing different shift systems, and additionally, by the poor methodological integrity of studies (Sallinen and Kecklund 2010).

Orth-Gomer was probably the first, and one of the few researchers who have conducted controlled intervention study to assess the effect of the change of shift rotation on coronary risk factors and to subjective well-being and sleep. Forty-five policemen worked 4 weeks each on their customary schedule with counter-clockwise rotation and on a new schedule with clockwise rotation. During the clockwise rotation of the shift schedule, their serum levels of triglycerides and glucose, systolic blood pressure and urinary excretion of catecholamines decreased and they reported longer and better sleep as compared to working on their old shift schedule with counter-clockwise rotation. The author concluded that adapting shift rotation to biological circadian rhythms has a favourable short-term effect, not only on subjective well-being but also on risk factors for ischemic heart disease (Orth-Gomer 1983).

Boggild and Jeppesen studied the effect of introducing regularity, few consecutive night shifts, more weekends off, and only 2 different types of shifts (day-evening or day-night) into shift scheduling on biomarkers of heart disease. After a 6-month follow-up, lipids and lipoproteins of the test individual changed favourably. The study suggested that scheduling based on ergonomic criteria is a possible means for reducing the risk of heart disease among shift workers (Boggild and Jeppesen 2001).

An intervention study by Hakola and Härmä explored the effect of a change in the speed and direction of shift rotation on the sleep and wakefulness of younger and older workers. A continuous three-shift schedule was changed from a slow backward rotating to a fast forward rotating system. Sleep problems decreased and alertness increased during the morning shifts. Among older workers both the subjective and objective quality of sleep improved indicating that a fast forward rotating shift schedule is more suitable for older workers than a slower backward rotating system (Hakola and Harma 2001). A controlled intervention study in Finnair maintenance confirmed these findings, the change from a slower backward to a very rapidly forward rotating shift system had positive effects on the sleep, alertness and well-being of especially the older shift workers (Harma, Hakola, et al. 2006).

In the study of Klein Hesselink et al., the changes in the roster were threefold: (1) from backward to forward rotating; (2) from three to two consecutive shifts; (3) the number of days off after the night shifts was changed from two to three. In the first year, absenteeism decreased and health indicators, such as fatigue decreased. The results were significantly more positive for the shift workers compared with day workers and older workers benefited more (Klein Hesselink et al. 2010).

Eldevik et al. found a significant positive association between quick returns (<11 hours off work between work shifts) and insomnia, excessive sleepiness, excessive fatigue and shift work disorder among Norwegian nurses (Eldevik et al. 2013). A longitudinal study on the same group of nurses conducted by Flo et al. revealed that quick returns increased the risk of shift work disorders and pathological fatigue and reducing the number of quick returns was related to a reduced risk of developing pathological fatigue (Flo et al. 2014).

An intervention study among female nurses (Jarvelin-Pasanen et al. 2013) demonstrated that the recovery of the autonomic nervous system from shift work can be promoted by the implementation of ergonomic recommendations. The main alteration was from backward to forward rotation, which was implemented by reducing quick returns. The heart rate variability parameters reflected increased parasympathetic activation and autonomic nervous system recovery.

In summary, means for decreasing the negative health effects of workhours include regulating overtime and excessive workhours, and increasing recovery by the introduction of sleep-promoting principles into shift rotation. The avoidance of quick returns and early morning shifts and night shifts, favouring the forward rotation of shift schedule and increasing possibilities for individual worktime control are measures that can be used to reduce the psychological, social and health problems of shift workers. Ergonomic recommendations with age-specific solutions on improving shift schedules help individuals to cope with shift work.

2.4.3.2 Workplace health promotion

The effectiveness of 31 lifestyle-focused random controlled intervention studies at workplaces on reducing the risk factors of cardiovascular disease summarized by Groeneveld et al. was inconsistent. Strong evidence was found for a positive effect on body fat and among populations 'at risk' on their body weights. There was no evidence for the effectiveness of interventions on physical activity, dietary factors, blood pressure, blood lipids and/or blood glucose. The authors concluded that intensive interventions targeted at populations with an elevated risk for CVD were the most profitable, whereas supervised exercise interventions appeared to be the least effective intervention strategy (Groeneveld et al. 2010).

The Balance@Work project in the Netherland aimed to develop, evaluate, and implement an occupational health guideline for the prevention of weight gain. The project did not improve employees' physical activity or body weight-related outcomes at a 6-month follow-up (Verweij et al. 2012). Based on 18-month follow-up data, the guideline was not effective in preventing weight gain, reducing CVD risk factors, or improving quality of life. Neither was the occupational health care guideline cost-effective (van Wier et al. 2013). The authors concluded that it may be worth evaluating an adapted, more intensive form of the guideline among high risk groups and more attention should be paid to maximizing attendance and satisfaction rates in order to improve their effects (Verweij et al. 2013).

The critical review by Neil-Sztramko et al. aimed to synthesize interventions that have been implemented among shift workers to reduce the chronic health effects of shift work. The studies were grouped into four intervention types: (1) shift schedule; (2) light exposure; (3) behavioural; (4) pharmacological. Several types of interventions had positive overall effects on chronic disease outcomes. There was, however, substantial heterogeneity among studies with respect to study sample, interventions, and outcomes. The findings suggested, that there is no "one size fits all" solution. Lifestyle habits may not improve spontaneously among shift workers as a result of e.g. shift schedule changes. Comprehensive, evidence-based approaches that include best practices in shift scheduling, a range of options to control exposure to light and dark, support for physical activity and healthy eating, as well as pharmacological agents, except for hypnotics, may be the best ways to improve health. The authors concluded that there is a need for further high-quality, workplace-based prevention research to be conducted among shift workers (Neil-Sztramko et al. 2014).

Schröer et.al. summarized the evidence from systematic reviews and meta-analyses, published from August 2006 to March 2012, of the effectiveness of different workplace health interventions for promoting healthy lifestyles, preventing diseases and reducing health care costs. Three systematic reviews found beneficial effects of workplace nutrition interventions on employees' dietary behaviour and three reviews found multi-component physical activity interventions to be effective in increasing employees' physical activity and fitness. The conclusion was that workplace health promotion interventions may improve physical activity, dietary behaviour and healthy weight and the best evidence is available for multi-component interventions (Schroer et al. 2014).

The systematic review of Montano et al. included 39 original papers of organisational-level workplace intervention studies at the primary prevention level, published between 1993 and 2012. Success rates were higher among more comprehensive interventions tackling material, organizational and work-time related conditions simultaneously. The median of follow-up times was one year. About half of the studies reported statistically significant intervention effects on health-related outcomes. The interventions focused mostly on burnout, absenteeism, musculoskeletal disorders, and depressive symptoms. Only two studies reported improvements in CVD outcomes (IHD and blood pressure) and one in sleep (Montano et al. 2014).

Nabe-Nielsen et al. investigated cross-sectional questionnaire data from 7,555 employees (2,064 shift workers) in Denmark to assess whether workplace health promotion reaches shift workers to the same extent as it reaches day workers. Information on the availability of and participation in workplace health promotion, as well as, on working hours, psychosocial work factors, and health behaviours were analysed. The study could not confirm that shift workers in general report a lower availability of and participation in workplace health promotion compared to day workers (Nabe-Nielsen et al. 2015).

New fatigue risk management regulations within the aviation industry (Gander et al. 2011) have forced it to develop educational programmes for flight crew members to help them cope with their irregular work schedules and accompanying circadian disruption. Van Drongelen et al. evaluated an mHealth intervention, using mobile technology, consisted of tailored advice regarding exposure to daylight, sleep, physical activity, and nutrition among 502 airline pilots. After six months, the intervention group showed significant improvements in levels of fatigue, sleep quality, strenuous physical activity, and snacking behaviour compared to the control group (van Drongelen et al. 2014).

In summary, when it comes to workplace health promotion, the best evidence is available for multi-component comprehensive interventions. The most profitable were intensive interventions targeted at populations with an elevated risk for CVD. New mobile technologies may be helpful for certain occupations. There is a need for further high-quality, workplace-based prevention research to be conducted among shift workers.

3. The aims of the study

The purpose of this study was to evaluate the screening and prevention of CVD risk factors and type 2 diabetes among the employees with varied working times in a large airline company. First, the effects of shift work and different shift systems on sleep-wakefulness and cardiovascular risk factors were studied. Second, the feasibility of risk screening and the effectiveness of lifestyle counselling on type 2 diabetes and cardiovascular risk factors along with health check-ups were investigated.

The specific aims of the study were

1. to assess risk factors of cardiovascular disease and risk of type 2 diabetes among airline employees with different working times
2. to investigate the effects of changes in shift systems on CVD risk factors and sleep-wakefulness
3. to test the feasibility of CVD risk screening in an airline health service
4. to evaluate the effectiveness of low-intensity lifestyle counselling being offered along with health check-ups

4. Methods

4.1 Study design and populations

This dissertation encompasses two longitudinal data of different interventions among the employees of the Finnish airline, Finnair; the data of the health check-up study (Figure 2a) and the data of the shift system change study (Figure 2b)

4.1.1 The health check-up study (Figure 2a)

The target group of the health check-up study was made up of 4169 airline employees. During the years 2006-2008, they were invited to a renewed health check-up according to age. A total of 2762 (66%) attended the health check-ups. Of these 2312 (84%) volunteered and were eligible to participate in the study. The exclusion criteria were previously diagnosed diabetes and pregnancy. The follow-up phase of the health check-up study was completed in 2009-2010. Of the 2199 invited employees 1465 (67%) participated in the follow-up study. Of these, 118 employees had retired or left the company at the end of the study and were excluded from the final data that comprised 1347 persons (men 54%).

With the cross-sectional baseline data of the health check-up study we studied

1. the association of shift work with the risk of type 2 diabetes and cardiovascular risk factors among the 2312 participants (Study I)
2. the association of former exposure to shift work with metabolic syndrome among 1811 (men 56%) full-time workers (Study II)
3. the interaction of age with shift rotation in relation to sleep–wakefulness and biomarkers of inflammation among 772 male 2- and 3-shift workers from the maintenance units of the airline company (Study IV)
4. the feasibility of T2D and CVD risk screening in the airline health service (Study I)

With the longitudinal data of the health check-up study we evaluated

1. the effect of the shift system change during the follow-up on biomarkers of inflammation (leukocytes and hsCRP) among 118 male 3-shift workers from the maintenance units of the airline company (Study IV)
2. the effectiveness of low intensity lifestyle counselling on decreasing the risk for T2D and CVD among 1347 participants who attended the follow-up (Study V)

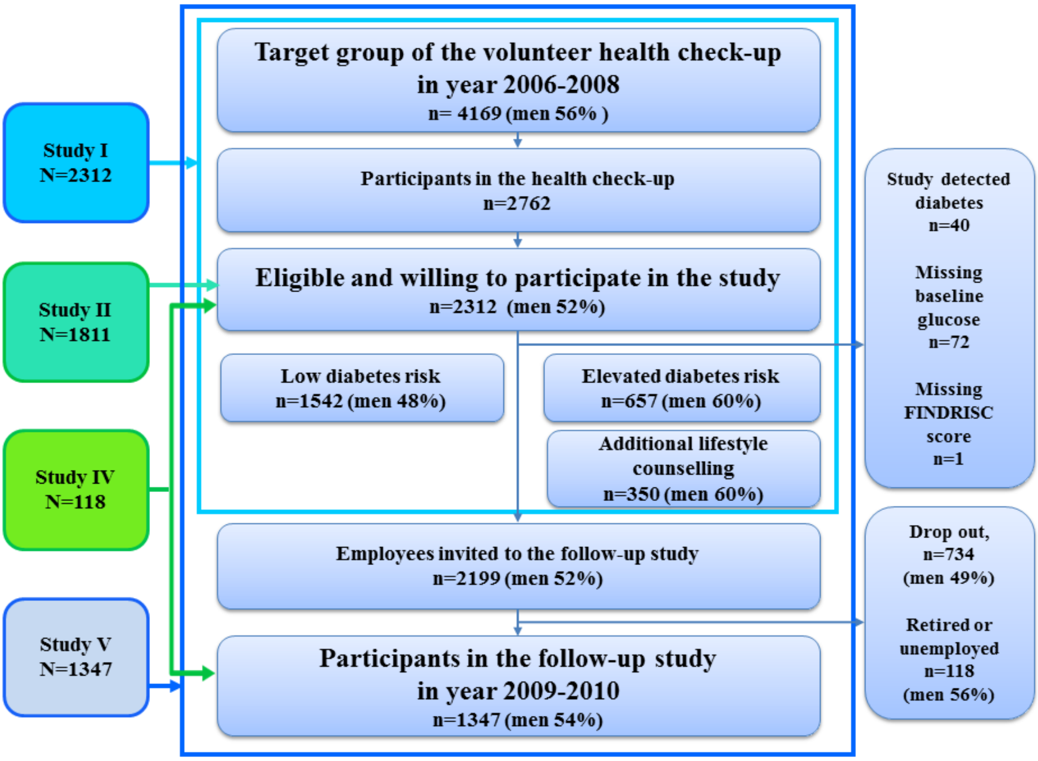

Figure 2a. The Health check-up study (Studies I, II, IV and V).

4.1.2 The shift system change study (Figure 2b)

The target group of the shift system change study consisted of 403 airline line maintenance workers, 343 of whom were working in a slowly backward rotating 3-shift work. Of these 89 men volunteered and were eligible to participate in the study. Random assignment to study groups was not possible and the participants were free to select their shift system from three choices: slowly backward rotating, flexible backward rotating or a rapidly forward rotating 3-shift system. Reasons for exclusion were the existence of any CVD or regular medication for blood pressure, high cholesterol, diabetes, or sleeping disorders. Complete data were available for 84 male participants, 40 of whom changed to a rapidly forward-rotating shift system, 22 changed to a more flexible shift system, and 22 persisted in the old shift system thus forming the reference group.

Together with the data of this shift system change study (Study III) we evaluated the effects of two separate changes in shift characteristics; a change in shift rotation (direction and speed) and a change in the flexibility (a combination of individual and company-based flexibility) of the shift system on employees’

1. alertness and
2. risk factors for CVD

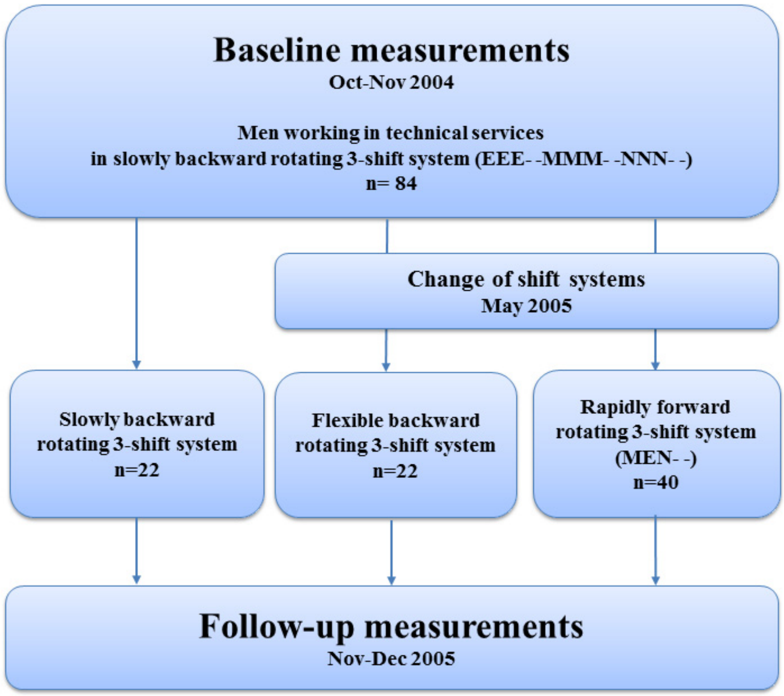

Figure 2b. The shift system change study (Study III).

4.2 Interventions

Two kinds of interventions were tested to promote workers' cardiovascular health and abilities to cope with shift work; changes in shift systems and lifestyle counselling.

4.2.1 Lifestyle counselling along health check-up

The health check-up process of the Finnair Health Services (FHS) was renewed in 2006. As the role of OHC in health promotion and evaluation of individual health risks had been emphasized by Finland's Ministry of Social Affairs and Health, the extended health check-up included the risk assessment of T2D and CVD as well as lifestyle counselling, which intensified according to the risk level (Figure 3).

During the baseline health check-up an occupational physician or an occupational health nurse discussed the results of the blood tests, clinical measurements and questionnaires with the employees and gave each of them general health advice. An individualized written health promotion plan was agreed upon. A special diabetes prevention website was launched providing information on physical exercise, healthy food choices, and general health advice with special attention given to shift work and its influence on sleep, lifestyle, and health.

In addition, those participants whose risk for T2D was assessed to be at least elevated (FINDRISC score 10-14, normal fasting glucose) were offered three one-hour lifestyle counselling sessions by a dietician. Those participants whose diabetes risk was assessed to be high (FINDRISC score ≥15, IFG or IGT) were offered three additional counselling sessions by a diabetes nurse. The same dietician gave dietary and lifestyle counselling to all participants. The counselling sessions by diabetes nurses were given by two professionally qualified persons.

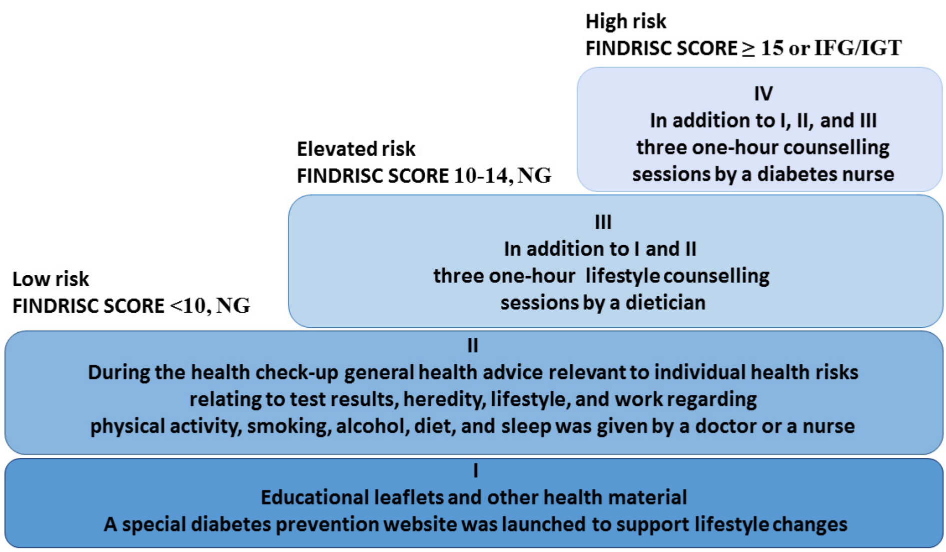

Figure 3. Lifestyle intervention according to the diabetes risk (NG normal fasting glucose, IFG impaired fasting glucose, IGT impaired glucose tolerance).

The FINDRISC score was used as the starting point of the discussion and the aims of all counselling were based on the Finnish Diabetes Prevention Study (J. Tuomilehto et al. 2001). The specific challenges related to shift work were taken into account and the discussion topics were individualized and based on personal needs regarding physical activity, sleep, smoking, alcohol consumption, and diet as reported in the dietary questionnaire. The aims were to endorse the participants' perception of risks related to their current lifestyle and to increase their motivation and abilities to achieve relevant changes in lifestyle with personalised short and long-term targets and self-selected practical goals (Prochaska et al. 1992). During the first year of the project, also group intervention (five 1½ hour counselling sessions by a dietician with varying themes) was offered to the participants at elevated diabetes risk (FINDRISC score $\geq$ 10). Participation in all lifestyle interventions was voluntary and the groups were not randomized.

4.2.2 Change of shift systems

The airline line maintenance unit is responsible for small and medium-sized maintenance duties round-the-clock. The old shift schedule in use was EEE – – MMM – – NNN – – (E = evening shift, M = morning shift, N = night shift, – = day off). All shifts were 8 hours long and the shift changing times were at 07:00, 15:00 and 23:00. In May 2005 two new shift systems were implemented in the line maintenance unit. A rapidly forward rotating shift system had a shift order of MEN – – (M from 06:00 to 16:00, E from 15:00 to 01:00, N from 21:00 to 06:00). The other new shift system was flexible with the direction of rotation and the order of the shifts basically the same as in the old shift system, but there was more variability in the shift schedule for operational reasons. Between the shift spells there were mostly three days off instead of the two of the old shift system. The night shift was always 7 hours long from 23:30 to 06:30, but the duration of morning shift varied from 10 to 13 hours (between 06:00 and 19:00) and the evening shift from 6 to 13 hours (between 13:00 and 02:00) depending on operational needs. Rosters were issued four weeks in advance and changes in the first two weeks' rosters were only possible with negotiation with the workers and with compensation. Based on mutual consent, the employer tried to fulfil the employees' wishes and needs regarding shift changes, holidays, or days off, thus allowing the workers some individual flexibility and control over their working hours in exchange for variability. The detailed description of the shift systems is presented in the original article (Study III).

4.3 Measurements

4.3.1 Clinical measurements

The clinical examination included measurements of height (without shoes to the nearest 1 mm), weight (in light indoor clothes to the nearest 100 g), and waist circumference (in the standing position midway between the lowest rib and iliac crest to the nearest 5 mm). Body mass index was calculated (kg/m^2). Blood pressure and heart rate were measured twice with an automatic device (Omron® M4-1) after a 5-minutes rest in the sitting position. At the baseline of the health check-up study (Studies I, II, IV) the measurements were completed by occupational nurses or physicians at Finnair Health Services (FHS). At the follow-up of the health check-up study (Studies IV, V), two trained study nurses, not employed by the FHS, performed the same clinical measurements. In the shift system change study (Study III), the same trained FHS nurse completed all the measurements at both phases. In the health check-up study, we could not standardize the blood pressure measurements and decided not to report the results.

4.3.2 Laboratory measurements

The participants of the health check-up study were advised to avoid smoking and vigorous activity for at least half an hour before the laboratory tests and it was emphasized they should not arrive for the tests after a night shift or when they were sick. When undergoing the laboratory tests, participants were asked to indicate if they had had an infectious disease during the past week (yes, no). As the blood samples of the shift system change study (Study III) were drawn in the workplace during a morning shift, the participants were supposed to be healthy and physical workload standardized. Blood tests were taken between 07:30 and 10:00 after a fasting period of 10 to 12 hours and included white blood cells (WBC), high-sensitivity C-reactive protein, plasma glucose, total cholesterol, high density lipoprotein, and triglycerides. Low density lipoproteins were calculated by the Friedewald formula. A 75-g oral glucose tolerance test (OGTT) was offered to those participants of the health check-up study whose diabetes risk was estimated to be high either based on the FINDRISC score ($\geq$15) or impaired fasting glucose ($\geq$6.1 mmol/l but <7.0 mmol/l). Glycosylated haemoglobin (HbA1c) was taken and analyzed only in the shift system change study (Study III).

At baseline of the health check-up study and at both phases of the shift system change study the laboratory tests were taken and analysed in the accredited laboratory of Mehiläinen Airport according to standard procedures using a Konelab 60i clinical chemistry analyser (Thermo Fisher Scientific, Ltd, Vantaa, Finland). Blood samples were centrifuged within 2 hours and analysed on the same day except for hsCRP, which was analysed twice weekly in a certified laboratory with a microparticle enhanced turbidometric immunoassay. EDTA blood samples for WBC were analysed by impedance measurement within 6 hours from drawing the sample with an Advia 120 cell counter (Siemens Medical Solutions, US).

At follow-up of the health check-up study the blood tests were analysed in the accredited laboratory of the Disease Risk Unit at the National Institute for Health and Welfare using an Architect ci8200 analyser (Abbott Laboratories, Abbott Park, IL, USA). Total cholesterol, HDL-cholesterol, triglycerides, and glucose were measured with enzymatic assays and hsCRP with an immunoturbidimetric method. EDTA blood samples for WBC were analysed by an ABX Micros 60 cell counter (Horiba Medical, Japan) within 2 hours of drawing the sample.

To assess and deal with measurement differences between the two laboratories, a set of 400 samples was analysed in both laboratories and the follow-up results for HDL-cholesterol and triglycerides were transformed accordingly to be commensurate with the baseline values. The bias between hsCRP measurements in the two laboratories was minimal and had no influence on the final results. It was not possible to assess the bias between WBC measurements in the two laboratories, because no data for instrument comparisons were available. However, the personnel of both laboratories regularly attended external quality assessment schemes to assure the stability of their results.

4.3.3 Questionnaires

The participants of the health check-up study filled in self-rated questionnaires with items about their education, work, working hours, sleep, diseases, medication, lifestyle habits, and the diabetes risk score FINDRISC (Lindstrom and Tuomilehto 2003). In the shift system change study the participants' educational level, work and working time were part of the study inclusion criteria and thus they were not required.

Education

In the health check-up study, the participant's educational level was graded by the highest education achieved using a seven-choice question (from comprehensive school to academic degree).

Working times

The participants were asked to indicate their current work (office work, planning work, marketing, managerial work, customer service, aircraft service work, maintenance work, storing work, cabin crew, and pilots), the current shift system (regular day work, 2-shift work, forward rotating 3-shift work, backward rotating 3-shift work, flexible 3-shift work, long-haul in-flight work, short/medium-haul in-flight work), number of night shifts a month, and whether they had previously worked in shifts.

In analyses of the health check-up study (Studies I and V) the working times were grouped as follows: a) regular day work, b) in-flight work (working on aviation duties as pilots or cabin attendants with diverse working hours), and c) non-flight shift work (neither regular day work nor in-flight work).

In analyses of the sub-study evaluating the effect of former shift work on MetS (Study II), working times were categorised into 5 groups: a) day work (work done between 06.00 and 18.00 hr.), b) former shift work (currently in day work), c) 2-shift work (morning and evening shifts), d) night shift work (3-shift work including night work for at least 3 hours between 23.00 and 06.00), e) in-flight work (irregular shift work with night work for at least 3 hours between 23.00 and 06.00 and/or time-lag for at least 4 hours).

In analyses of the sub-study evaluating the age-associated relationship between the shift system and sleep-wakefulness and inflammation (Study IV) working times were categorized as follows: a) day work (any job with working time between 06:00 -18:00 and free weekends), b) 2-shift work (day and evening weeks follow one after another with free weekends), c) rapidly forward rotating 3-shift work (shift order MEN – –), d) slowly backward rotating 3-shift work (shift order EEE – – MMM – – NNN – –), and e) flexible 3-shift work (the shift order basically the same as in the previous shift system, but contained more variation in rosters allowing both company-based and individual flexibility).

In the shift system change study working times were equal to c, d, and e, described in the previous paragraph.

Lifestyle habits
Dietary factors were requested using self-rated questionnaires (validated afterwards by Hemiö et al.) including questions about alcohol, coffee, milk products, fruits, vegetables, sugar and quality of fat. Information about dietary fibre was asked about more exactly in the health check-up study (Hemio et al. 2014). Smoking was coded as current smoker or non-smoker. Alcohol consumption was measured as the number of 12 g units/week. At-risk alcohol consumption was defined for men as >40g/day and for women as >20g/day according to the Finnish Current Care Guideline. In the health check-up study physical activity was requested using a four-choice question on weekly physical activity during leisure time (1=little/hardly any to 4=several times /competitive type). Active lifestyle was defined as practising non-sweat physical activity at least 4 hours weekly and a sedentary lifestyle was less than that. In the shift system change study (Study III) leisure time physical activity (LTPA) was assessed by the modified International Physical Activity Questionnaire (IPAQ) (Craig et al. 2003), which requested the number of physical activity sessions per week and the number of minutes per session. The intensity of LTPA was enquired with examples of strenuous, moderately strenuous, and light intensity physical activity.

Sleep and wakefulness were investigated with a questionnaire containing the following questions: 1) “How many hours do you usually sleep per 24 hours?”, 2) “How many hours of sleep do you need to be alert the next day?”, 3) “How often have you had difficulties to fall asleep during the past three months?”, 4) “How often have you awoken at night during the past three months?”, 5) “How often do you feel fatigue/tired during the day time?”, 6) Epworth Sleepiness Scale´s (Johns 1991) nine questions (ESS). Sleep loss was assessed as the difference between the hours of self-rated need for daily sleep (question 2) and the received daily amount of sleep (question 1) (Hublin et al. 2001). The insomnia symptom questions 3 and 4, and the slightly modified question 5 from the Basic Nordic Sleep Questionnaire (Partinen and Gislason 1995) were self-rated using a Likert-type scale (1=never or less than once a month to 5=daily or almost daily). The health check-up study included an additional question "How harmful do you feel your current working time is to your sleep-wakefulness?". Answers to this modified question from the Standard Shiftwork Index (Barton et al. 1995), were asked to self-rate using the scale: 1= not at all harmful, 2= a little harmful, 3= quite harmful, 4= very harmful.

FINDRISC score and metabolic syndrome

The Finnish diabetes risk score FINDRISC comprises 8 categorized and rated questions (age, body mass index, waist circumference, physical activity, consumption of fruit and vegetables, hypertension medication, history of high blood glucose, and family history of diabetes) and gives an estimate of the subject's probability of getting diabetes in 10 years (Lindstrom and Tuomilehto 2003). A FINDRISC score <10 with normal fasting glucose (<6.1 mmol/l) was considered to denote low diabetes risk and a score value 10-14 with normal glucose was assessed to mean elevated risk. A score value ≥15 or impaired fasting plasma glucose (fP-glucose ≥6.1 but <7.0 mmol/l) or impaired glucose tolerance (2-hour glucose in the OGTT ≥7.8 but <11.1 mmol/l) was considered to denote high diabetes risk. Metabolic syndrome was defined according to the IDF criteria (Alberti et al. 2005) listed in Table 1.

4.4 Ethical aspects

The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the studies and all subjects gave their written informed consent. Participation in all studies and interventions was voluntary. The lifestyle intervention offered along with the health check-up was formulated in accordance with the Finnish Current Care Guidelines. In the health check-up study all employees received general verbal health advice relevant to the individual risk profile and written information of healthy lifestyle by a doctor or a nurse. Employees at elevated diabetes risk (FINDRISC ≥10) were offered additional counselling by a dietician and the high risk individuals (FINDRISC ≥15 or IFG or IGT) were moreover referred to a diabetes nurse. Persons with study-detected diabetes were referred to diabetes clinics and their data were removed from the study data in further analyses.

The data of Studies I, II, IV and V were stored on the server of the National Institute for Health and Welfare with an individual study identification code. The links between the study identification codes and the subjects' personal ID codes were confidentially and securely stored by Finnair Health Services. Participants in the health check-up study gave their written informed consent to link the study data relating to the clinical measurements and blood tests to their personal health care data. The data was transferred to the

Finnish Institute of Occupational Health with the study identification code for the statistical analyses. Study III data were stored confidentially and securely by Finnair Health Services with the study identification codes separate from the health records, except for the clinical measurement and blood test data, which were linked to the personal health care data with the written permission of the participants. The data of these studies will be destroyed after being analysed and the results published.

4.5 Statistical methods

With the cross-sectional baseline data of the health check-up study (Study I), differences between groups based on sex, diabetes risk score, and working time and background factors for participating in lifestyle interventions were evaluated with the chi-square test, t-test and analysis of covariance. With the longitudinal follow-up data of the health check-up study (Study V), changes of the CVD risk factors in relation to participating in lifestyle intervention given by a diabetes nurse and/or a dietician were analysed with repeated measures analysis of variance and the paired sample t-test for continuous variables and chi-square or Fischer's exact test for categorical variables. Age and education were used as covariates. Log-transformed values for triglycerides and high sensitivity C-reactive protein were used due to the non-normal distributions of these variables. The counselling sessions of the dietician and the diabetes nurse were combined into a single variable in the analysis.

With the cross-sectional baseline sub-data of the health check-up study (Study II) the association between metabolic syndrome and shift work was evaluated with the following analyses. First, differences in control variables between the working time groups were tested with analysis of variance and the chi-square test, with day work as the reference group. Then the relationship between each control variable and the MetS was evaluated with multiple logistic regression analysis and odds ratios with 95% confidence limits were calculated for the risk of MetS in working time groups. The tested models were adjusted for age and all the covariates. Alcohol consumption was log-transformed prior to the analyses.

With the other cross-sectional baseline sub-data of the health check-up study (Study IV), the effect of shift system, age, and their interactions on sleep and wakefulness, and the biomarkers of inflammation were evaluated with multivariable analysis of variance. The effects of shift system, age and their interactions on how harmful (quite, very) employees experienced their working times were for their sleep and wakefulness were estimated with multivariable logistic regression analysis. Differences between sleep and wakefulness in the age groups were tested between the 3-shift work groups and also between day work and each shift work group separately. With the longitudinal follow-up sub-data, the effect of the shift system change on the biomarkers of inflammation (leukocyte count and hsCRP) was estimated with repeated measures analysis of variance. The models were adjusted for recent infectious diseases and only data with hsCRP values <10 were used in analyses. Log-transformed values for hsCRP, leukocyte count and ESS were used in the statistical analyses. The “Problems to fall asleep” variable was square root-transformed.

With the longitudinal data collected in the shift system change study (Study III), differences between the shift systems were evaluated with repeated measures analysis of variance. Variables in the models were time, shift system, interaction of time and shift system, age at baseline, smoking, and alcohol consumption. The distribution of caffeine and alcohol consumption and physical activity were skewed and ranks were used instead of the original values for these outcomes.

The statistical analyses were calculated using the SAS (SAS Institute Inc., Cary, NC, USA) program for Studies III and IV. The SPSS (SPSS Inc., Chicago, IL, USA) program was used for all other statistical analyses except for the confidence intervals for the changes of dichotomous variables of Study V, which were analysed by the McNemar test using MedCalc (Professional Medical Calculator) statistical software.

5 Results

5.1. Risk of cardiovascular disease and diabetes among employees with different working times

5.1.1 Risk factors of CVD and risk for T2D in working time groups

At baseline of the health check-up study (Study I) 36% of all participants were regular day workers, 35% non-flight shift workers, and 29% in-flight workers. In the target group the percentages were 33%, 39%, and 28%, respectively. In the health check-up 40 new cases of diabetes were found and excluded from analysis. The working time groups differed in age and education, day workers being the oldest and non-flight shift workers the least educated groups. After adjusting for age and education, the observed differences in CVD risk factors were rather small between the day workers and non-flight shift workers. The female in-flight workers stood out from the rest (Table 6).

Table 6. Characteristics and risk factors of the Study I participants (mean ± SD) according to sex and working time groups.

	Men					Women				
	Regular day work n=471 (39.3%)	**Non-flight shift work** n=581 (48.5%)	**In-flight work** n=147 (12.3%)	p-value[1]	p-value[2]	**Regular day work** n=351 (31.5%)	**Non-flight shift work** n=229 (20.6%)	**In-flight work** n=533 (47.9%)	p-value[1]	p-value[2]
Age, years	46.8 (9.3)	43.9 (8.6)†††	42.6 (8.6) †††		<0.001	46.6 (8.3)	43.3 (8.7) †††	42.6 (8.8) †††		<0.001
Education, high[3], %	61.8	12.7***	69.6***	<0.001		62.5	48.8**	74.9***	<0.001	
Smoking, %	20.0	26.2*	17.1	0.019	0.239	22.3	26.8	12.7**††	<0.001	<0.001
Alcohol, units/week	7.6 (8.6)	6.4 (6.0)	6.1 (5.5)	0.058	0.072	3.5 (3.7)	3.2 (4.2)	3.2 (3.3)	0.998	1.000
Sedentary lifestyle[4], %	18.2	21.2	10.5	0.014	0.051	17.8	15.7	6.2***†††	<0.001	<0.001
BMI, kg/m²	27.1 (3.8)	27.1 (4.0)	25.8 (3.3)** ††	0.002	0.012	25.6 (4.6)	25.5 (4.9)	23.1 (3.1)*** †††	<0.001	<0.001
Systolic BP, mmHg	143 (17)	143 (16)	137 (15)** †	<0.001	0.008	135 (19)	130 (17)**	129 (18)** ††	0.022	0.027
Diastolic BP, mmHg	89 (12)	88 (11)	85 (10)	0.020	0.144	84 (11)	83 (11)	81 (10)	0.090	0.090
fP-glucose, mmol/l	5.6 (0.8)	5.5 (0.6)	5.7 (0.5)	0.087	0.086	5.3 (0.6)	5.2 (0.5)	5.2 (0.5)	0.660	0.190
fP-cholesterol, mmol/l	5.2 (0.9)	5.2 (1.0)	5.2 (1.2)	0.695	0.823	5.1 (0.9)	5.0 (0.9)	5.0 (0.9)	0.637	0.906
FINDRISC score	7.4 (4.7)	6.8 (4.3) ††	5.6 (4.3)* †	0.035	0.037	7.6 (4.8)	7.0 (4.8)	4.9 (4.0)*** †††	<0.001	<0.001

[1] Pairwise test comparing non-flight shift work and in-flight work to regular day work, age-adjusted. (*** $p<0.001$, ** $p<0.01$, and * $p<0.05$).

[2] Pairwise test comparing non-flight shift work and in-flight work to regular day work, adjusted for age and education. (††† $p<0.001$, †† $p<0.01$, and † $p<0.05$). Log-transformed values for triglycerides and high sensitivity CRP were used in pairwise tests.

[3] Education high level: college-level training, polytechnic or academic degree of education.

[4] Sedentary lifestyle: less than 4 hours weekly leisure time non-sweat physical exercise.

Among men, after adjustment for age and education, the non-flight shift workers had slightly higher hsCRP (1.85 ± 3.64 vs. 1.52 ± 2.68 mg/l) but lower FINDRISC score compared with male day workers. In-flight workers had significantly lower BMIs, waist circumferences (91.3 ±9.6 vs. 96.1 ± 11.2 cm), systolic blood pressures, plasma triglyceride levels (1.18 ± 0.57 vs. 1.34 ± 0.74 mmol/l) and also FINDRISC scores compared with male day workers.

Among women, after adjustment for age and education, the non-flight shift workers had clearly higher hsCRP (2.74 ± 5.53 vs. 2.01 ± 4.19 mg/l) but lower systolic blood pressures compared to the day workers. Female in-flight workers were more often smokers, but fewer of them had a sedentary lifestyle, their HDL-cholesterol values were higher (1.92 ± 0.47 vs. 1.76 ± 0.46 mmol/l) and their BMIs, waist circumferences (78.2 ± 8.4 vs. 83.5 ± 11.9 cm), systolic blood pressures, plasma triglyceride levels (0.87 ± 0.46 vs. 0.96 ± 0.49 mmol/l), hsCRP values (1.38 ± 2.78 vs. 2.01 ± 4.19 mg/l), and FINRDISC scores were significantly lower compared with the day workers.

5.1.2 Former shift work and metabolic syndrome

The prevalence rate of IDF-defined MetS, analysed from the baseline sub-data of 1811 participants of the health check-up study (Study II), was 28.5%. The risk of MetS increased with age (6% per year) and was 2.4 times higher among men compared to women, 40% higher among current smokers compared with non-smokers, and 1.8 fold higher among participants with low education levels compared to those with high education levels. Table 7 gives the results of comparisons between working time groups (day work vs. former shift work, 2-shift work, night shift work, and in-flight work) for the IDF-defined MetS, separately for men and women.

Table 7. Working times and prevalence of International Diabetes Federation (IDF) defined MetS.

	Former shift work vs. day work		2-shift work vs. day work		Night shift work vs. day work		In-flight work vs. day work	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
				Men				
Age-adjusted	2.13	1.35-3.37	1.64	1.06-2.55	1.51	0.95-2.34	1.21	0.70-2.01
Full model[1]	2.00	1.26-3.19	1.48	0.93-2.24	1.37	0.84-2.22	1.33	0.76-2.33
				Women				
Age-adjusted	1.31	0.74-2.32	1.36	0.77-2.39	1.12	0.48-2.60	0.64	0.39-1.07
Full model[1]	1.51	0.83-2.77	1.42	0.78-2.59	1.31	0.54-3.17	0.84	0.48-1.46

[1]Adjusted for age, education, physical activity, alcohol use, smoking, and insomnia symptoms.

Among the men, compared with day workers, former shift workers had over 2-fold age-adjusted risk of MetS and further adjustments did not influence the result. There was also an association between current 2-shift work and MetS, even though further adjustment diluted this association. Compared to day workers MetS was not more common among current night shift workers. In additional analyses (not shown in Table 5), there were associations between former night shift work and MetS, as well as other types of former shift work and MetS (age-adjusted OR 2.05 [95% CI 1.24, 3.36] and 2.32 [95% CI 1.26, 4.30], respectively) among men.

Among women, the odds ratios were systematically lower compared to men. There were no significant differences in the prevalence of the MetS between day work and shift work observed in the comparisons among women.

5.2 Association of the change of shift systems with CVD risk factors

The shift system change study (Study III) carried out on male aircraft maintenance participants showed that, the changes in systolic blood pressure were different between the three study groups (p=0.049). During the follow-up period of 7 to 8 months, systolic blood pressure decreased among the participants who changed to the flexible backward rotating shift system compared to those who remained in the old slowly backward rotating shift system with no flexibility. Mean systolic blood pressure decreased by 6 mmHg in the group with the flexible shift system, increased by 2.5 mmHg in the group with the rapidly forward shift system, but remained unchanged for those in the old shift system (Figure 4a). As depicted in Figure 4b, a similar trend was also observed for heart rate. In further analyses, comparing the flexible shift system to the old shift system the changes in heart rate had a decreasing trend (p=0.056). The changes in diastolic blood pressure were not significant.

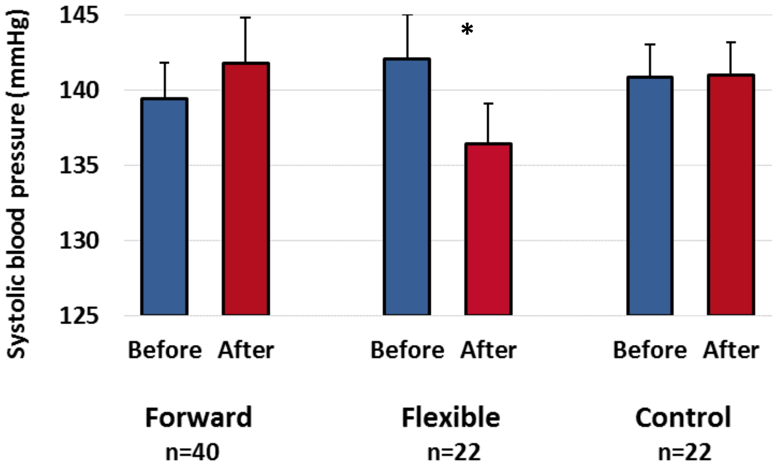

Figure 4a. The effect of a change of shifts on systolic blood pressure (mean, ± SE) among the group with a rapidly forward rotating shift system (Forward), the group with a more flexible shift system (Flexible), and among the group with the old shift system (Control). All groups started with a slowly backward rotating shift system with no flexibility. (* p=0.049).

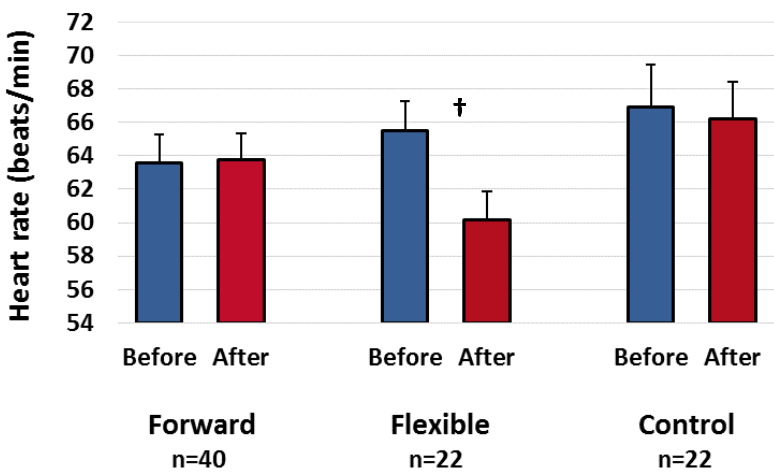

Figure 4b. The effect of a change of shifts on heart rate (mean, ± SE) among the group with a rapidly forward rotating shift system (Forward), the group with a more flexible shift system (Flexible), and among the group with the old shift system (Control). All groups started with a slowly backward rotating shift system with no flexibility. (†p=0.056).

Compared to the old shift system, the change to the flexible shift system or to the rapidly forward rotating shift system had no influence on shift workers' BMIs, waist circumferences, cardiovascular risk factors (lipids, fasting glucose, HbA1c), inflammatory biomarker levels (hsCRP), dietary factors (fibre, caffeine, quality of fat) nor their health habits (alcohol consumption and leisure time physical activity).

5.3 Age-dependent association of shift systems with sleep-wakefulness and biomarkers of inflammation

5.3.1 Interaction between shift system and age with sleep-wakefulness

Table 8 shows the results analysed with the sub-data of the health check-up study (Study IV) comprising male 2-shift and 3-shift workers from the aircraft maintenance units of the company. The 3-shift workers reported more problems to fall asleep compared to day workers (p-values $\leq$ 0.001) and older workers tended to have more problems to fall asleep (main effect p=0.066) and awakenings during sleep (main effect p=0.059). Based on the post hoc tests, day workers' sleep was shorter among older workers than among younger workers, while in the forward rotating 3-shift work, older workers slept longer than younger workers (post-hoc interaction p=0.007). In addition, younger employees needed more sleep than older employees in day work, while in the forward rotating 3-shift system the sleep need of older workers was greater than the sleep need of younger workers (post-hoc interaction p=0.040).

Compared to day work, after adjustment for age and the interaction between age and shift system, the OR for the employees' feeling that their current shift system was harmful to their sleep and wakefulness was 13.20 (main effect p<0.001) for the rapidly forward rotating shift system, 22.85 (main effect p<0.001) for the flexible shift work system, and 43.37 (main effect p<0.001) for the slowly backward rotating shift system. Comparisons between the 3-shift systems indicated that employees in the slowly backward rotating shift system felt their working time more harmful for their sleep-wakefulness compared to employees in the rapidly forward rotating shift system (OR 3.29, main effect p=0.036). The flexible shift system did not differ from the rapidly forward rotating shift system (OR 1.73, main effect NS).

Table 8. Sleep and wakefulness of male day and shift workers aged <45 or ≥45 years.

	Day work		2-shift work		3-shift work forward		3-shift work flexible		3-shift work backward		p-value[1]		
											shift system	age	inter-action
	<45 yrs (n=190)	≥45 yrs (n=263)	<45 yrs (n=57)	≥45 yrs (n=61)	<45 yrs (n=20)	≥45 yrs (n=41)	<45 yrs (n=75)	≥45 yrs (n=22)	<45 yrs (n=16)	≥45 yrs (n=27)			
	Mean (SD)		*Mean (SD)*		*Mean (SD)*		*Mean (SD)*		*Mean (SD)*				
Sleep length, hours	7.3 (0.82)	7.0 (1.00)	7.3 (0.71)	7.3 (0.75)	7.1 (0.89)	7.5 (1.01)	7.3 (0.84)	7.1 (1.30)	7.3 (1.25)	7.3 (1.03)			0.030[2]
Sleep need, hours	7.9 (0.96)	7.5 (0.99)	7.7 (1.04)	7.8 (0.75)	7.8 (1.30)	8.0 (1.12)	7.6 (0.99)	7.7 (1.70)	7.9 (1.39)	7.6 (0.97)			0.043[3]
Problems to fall asleep[4]	1.8 (0.90)	1.8 (0.93)	1.6 (0.73)	2.0 (0.93)	2.3 (0.97)	2.2 (0.98)	2.1 (0.92)	2.5 (1.22)	2.2 (0.91)	2.4 (1.22)	<0.0001	(0.066)	
	Number (%)		*Number (%)*		*Number (%)*		*Number (%)*		*Number (%)*				
Employees who feel their current shift system to be harmful to their sleep and wakefulness	2(1)	2(1)	5 (9)	5 (9)	2 (10)	5 (12)	12 (16)	4 (19)	4 (25)	9 (33)	<0.0001		

[1] Analysis of variance for continuous variables, logistic regression for categorical variables. Effects of shift system, age and their interaction.

[2] In post hoc test significant age-interactions were between day work and 2-shift work (p=0.034), between day work and forward rotating 3-shift work (p=0.007), and a trend between forward rotating 3-shift work and flexible 3-shift work (p=0.071).

[3] In post hoc test significant age-interactions were between day work and 2-shift work (p=0.017), between day work and forward rotating 3-shift work (p=0.045), and a trend between day work and flexible 3-shift work (p=0.096).

[4] Scale 1-5: 1=never or less than monthly, 2=less than weekly, 3=once or twice a week, 4=three to five times a week, 5=daily or almost every day.

5.3.2 Effect of the shift system change on alertness

The results of the shift system change study (Study III) carried out on male aircraft maintenance participants, indicated that the change of shift system influenced shift workers' alertness. The mean number of days per week for which the workers reported sleepiness decreased in the group which changed to the rapidly forward rotating shift system, but increased slightly among the workers who persisted in their old slowly backward rotating shift system or changed to the flexible shift system (Figure 5).

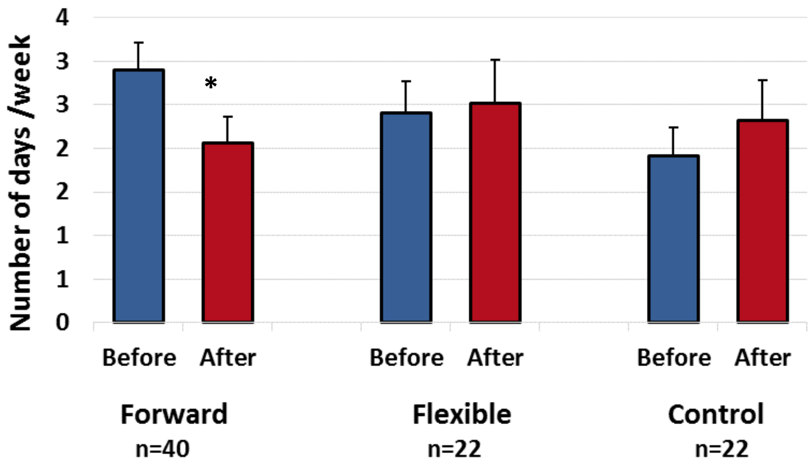

Figure 5. The effect of a change of shifts on the number of days/week (mean, + SE) with sleepiness among the group with a rapidly forward rotating shift system (Forward), the group with a more flexible shift system (Flexible), and the group with the old slowly backward rotating shift system (Control). All groups started with a slowly backward rotating shift system with no flexibility. (*p=0.023).

Daytime sleepiness showed a declining trend when all three shift systems were compared to each other ($p = 0.056$). In further analyses, the changes in daytime sleepiness were significantly different between the rapidly forward rotating and the old backward rotating shift systems ($p = 0.023$). Congruent with this, the ESS score and caffeine consumption declined among the workers who changed to the forward rotating shift system, though not significantly compared to the control group.

5.3.3 Interaction of the shift system and age with biomarkers of inflammation

Analyses with the cross-sectional sub-data of the health check-up study, comprising male 2-shift and 3-shift workers in the aircraft maintenance (Study IV), showed no significant main effects of the shift system (day work, 2-shift work, rapidly forward rotating 3-shift work, flexible backward rotating 3-shift work, and slowly backward rotating 3-shift work) on the biomarkers of inflammation (leukocytes and hsCRP). However, in the leukocyte counts there was an interaction trend between the shift system and age (p=0.067). Figure 6 shows that leukocyte count for day workers was higher among older employees, while in 2-shift work the age difference was inversed (post-hoc interaction p=0.016). In addition, within the 3-shift systems, forward rotation shift workers' leukocyte counts seemed to be lower in the older age group compared to younger workers, but this age-difference in leukocytes did not significantly depend on the shift system.

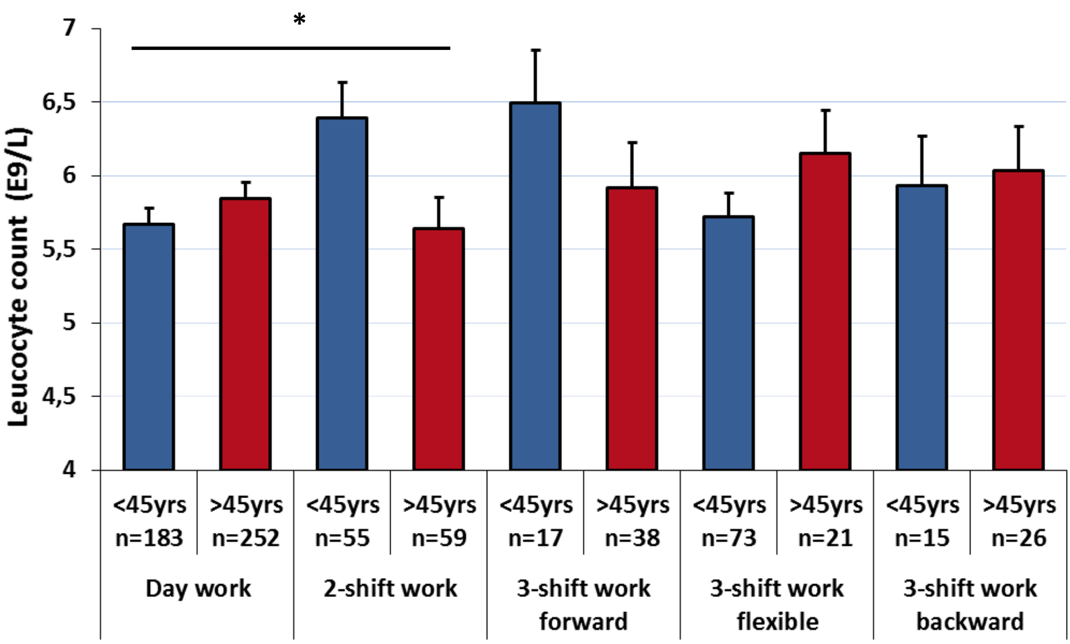

Figure 6. Leukocyte count, E9/L (mean, +SE) of male day and shift workers aged <45 or ≥45 years. (Cross-sectional data, cases with hsCRP≥10 mg/L not included) (* p=0.016 for post hoc interaction of age and shift system).

5.3.4 Effect of the shift system change on biomarkers of inflammation

Figure 7 shows how the leukocyte count decreased as the 3-shift workers changed from the old or flexible backward rotating shift systems to the rapidly forward rotating shift system during the follow-up period in Study IV. However, these associations did not reach statistical significance in this sample. Neither were there significant associations in hsCRP with the change in shift systems.

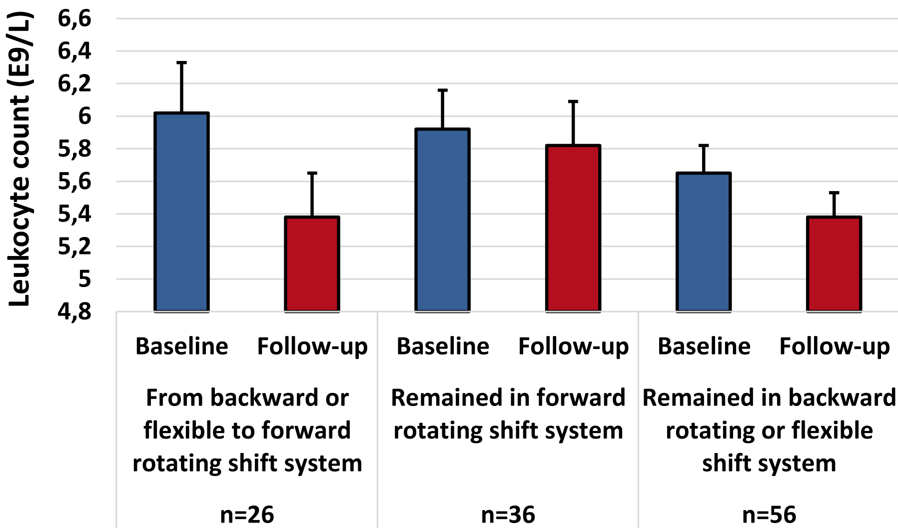

Figure 7. Leukocyte count, E9/L (mean, +SE) of male shift workers who changed from flexible 3-shift work or backward rotating 3-shift work to the forward rotating shift system or remained in their old shift systems. (Longitudinal data, cases with hsCRP≥10 mg/L not included) (Leukocyte count change was not statistical significant in any group).

5.4 Feasibility of the risk screening of CVD and T2D in the airline health service

5.4.1 Characteristics and risk factors of the participants of the health check-up study

Of the target group (n=4169) of the health check-up study (Study I) 2762 employees (66%) attended the health checks and of these 2312 (84%) were eligible for the study. The participants' characteristics and risk factors according to gender and working time groups at baseline are presented in Table 6 above.

The FINDRISC score as the first step screening method not only efficiently revealed any risk for diabetes, but also risk for metabolic syndrome. Of the participants with elevated FINDRISC scores (10-14) 51% had

IDF-defined MetS, and of those with high scores (≥15) as many as 70.5% had MetS. Also other studied CVD risk factors correlated well with the FINDRISC score as shown in Table 9.

Table 9. Characteristics and risk factors of participants (per cent or mean ± SD) according to diabetes risk score (FINDRISC).

	Low risk score <10 n=1698 (75.7 %)	**Elevated risk score 10-14** n=412 (18.4 %)	**High risk score ≥15** n=132 (5.9 %)	p-value[1]
Men, %	51.4	54.1	54.5	0.504
Age, years	43.1 (8.8)	48.9 (7.6)***	51.0 (7.0)***	<0.001
Education, high level[2], %	49.2	39.1***	40.5***	<0.001
Smoking, %	19.6	22.1	22.5	0.448
Alcohol, units/week	5.0 (5.6)	5.6 (6.1)	6.9 (9.6)**	0.008
Sedentary lifestyle[3], %	11.4	27.0***	29.9***	<0.001
Body Mass Index, kg/m^2	24.6 (3.4)	28.9 (4.5)***	30.6 (4.5)***	<0.001
Systolic blood pressure, mmHg	135 (18)	143 (19)***	147 (19)***	<0.001
Diastolic blood pressure, mmHg	84 (11)	90 (10)***	92 (12)***	<0.001
fP-glucose, mmol/l	5.3 (0.6)	5.6 (0.6)***	5.9 (0.9)***	<0.001
Total cholesterol, mmol/l	5.1 (0.9)	5.3 (1.0)***	5.2 (0.9)*	<0.001
MetS[4], %	16.6	51.0***	70.5***	<0.001

[1] F-test for continuous and chi-square test for categorical variables. The low risk score group was compared pairwise with moderate and high risk score groups (*** p<0.001, ** p<0.01, and * p<0.05). Log-transformed values for triglycerides and high sensitivity C-reactive protein were used in analyses.
[2] Education high level: college-level training, polytechnic or academic degree of education.
[3] Sedentary lifestyle: less than 4 hours weekly leisure time non-sweat physical exercise.
[4] Metabolic Syndrome according to the IDF criteria.

5.4.2 Characteristics associated with participation in the follow-up of the health check-up study

Men participated in the follow-up (Study V) better than women (68 vs. 62%, p=0.005). The participants were three years older and their fasting plasma glucose levels were lower compared to the non-participants (p<0.01). Day workers and non-flight shift workers participated in the follow-up more eagerly than in-flight workers (p<0.001). Among men, being married/cohabit and a non-smoker, and among women, higher FINDRISC score and shorter daily sleep time were the background characteristics, which associated with eager participation in the follow-up.

5.4.3 Characteristics associated with attendance in lifestyle intervention

At the baseline, 15.1% of all participants were high diabetes risk individuals (FINDRISC score ≥15, IFG or IGT) and 14.9% had elevated risk (FINDIRSC score 10-14 and normal glucose). Of these 60% and 59%, respectively, attended lifestyle counselling provided by a diabetes nurse and/or a dietician. Individual counselling was preferred to small-group counselling, which was offered only on the first year because of the low participation rate. Men and women who were offered lifestyle counselling at the baseline health check-up, attended counselling sessions equally (p=0.524). As presumed, FINDRISC score, waist circumference, and BMI associated strongly with participation (p<0.01). Also sedentary lifestyle, depressive symptoms and perception of sleeping problems or stress affecting work ability associated with participation among both genders (p<0.05). Older age, being single, more years in shift work and poor work ability associated with participation among men (p<0.05), while regular day work, physically light work, daytime fatigue and the feeling that personal needs were not being taken into account in rosters increased participation among women (p<0.05).

Table 10 shows the attendance at lifestyle counselling sessions given by the dietician or/and diabetes nurse among those elevated and high diabetes risk individuals who participated in the follow-up study (Study V). The attendance frequency at counselling sessions was higher among men compared to women in the group with elevated diabetes risk (p= 0.014) and in the group with both elevated and high diabetes risk (p=0.029).

Table 10. Attendance at lifestyle counselling sessions by a dietician and a diabetes nurse among the participants of the follow-up study (Study V) according to baseline diabetes risk (per cent and count).

	Attendance at lifestyle counselling						
	Elevated risk[1]			High risk[2]			Elevated and high risk[3]
	No	Once	More than once	No	Once	More than once	At least once
Men and women who attended the follow-up, % (n)	**32.9** (69)	**43.3** (91)	**23.8** (50)	**45.8** (88)	**18.2** (35)	**35.9** (69)	**60.9** (245)
Men who attended the follow-up, % (n)	**31.4** (32)	**37.3** (38)	**31.4** (32)	**47.8** (65)	**19.1** (26)	**33.1** (45)	**59.2** (141)
Women who attended the follow-up, % (n)	**34.3** (37)	**49.1** (53)	**16.7** (18)	**41.1** (23)	**16.1** (9)	**42.9** (24)	**63.4** (104)

[1]FINDRISC score 10-14 and normal fasting glucose. Counselling by a dietician was offered.
[2]FINDRISC score $\geq$15 or IFG or IGT. Counselling by a dietician and a diabetes nurse was offered.
[3]FINDRISC score $\geq$10 or IFG or IGT. Counselling by a dietician and a diabetes nurse was offered.

5.5 Effectiveness of low intensity lifestyle counselling offered along with health check-ups

5.5.1 Effect of lifestyle intervention on CVD risk factors

As shown in Table 11, the group of men with elevated and high diabetes risk (FINDRISC ≥ 10, IFG or IGT) lost some weight compared with the low risk men (FINDRISC <10 and normal glucose) who gained weight. The difference in weight change between these groups was significant (p=0.002), but adjustment for age attenuated the significance (p=0.092). The elevated and high risk group of men succeeded in reducing their weight at least 5% twice as often as the low risk men, and the difference in weight reduction between these groups was significant (age-adjusted p=0.010). Among the elevated and high risk men also total cholesterol decreased -0.04 (95% CI -0.14, 0.06) mmol/l but increased among the low risk men 0.02 (95% CI 0.14, 0.27) mmol/l. The difference of the change in cholesterol level between these groups was significant (p<0.001, age-adjusted p=0.002, not shown in the table).

The proportion of physically inactive employees remained unchanged in the low diabetes risk group. However, sedentary lifestyle tended to decrease among the men with elevated and high diabetes risk (p=0.052) and compared to the men with low risk the differences in the changes in physical activity between the risk groups were statistically significant (age-adjusted p=0.017). During the follow-up, the FINDRISC score increased a little among both genders in the low risk group as well as in the elevated and high risk groups. Among men the difference between the risk groups was not significant (Table 11). Among women the score increased by 1.04 (95% CI 0.57, 1.39) in the low risk group and by 0.29 (95% CI 0.82, 1.26) in the elevated and high risk group, and the difference between the risk groups was statistically significant (age-adjusted p=0.001).

Table 11. Weight change, weight loss 5% or more, change of sedentary lifestyle and FINDRISC score during follow-up among the low diabetes risk men (FINDRISC <10 and normal glucose) and among the elevated and high diabetes risk men (FINDRISC ≥ 10, IFG or IGT).

	Low risk men (n=486)	**Elevated and high risk men** (n=238)	p-value[1]	p-value[2]
Weight change (kg), mean (95% CI)	0.84 (0.52, 1.16)	-0.13 (-0.71, 0.46)	0.002	0.092
Weight loss 5% or more, proportion of men, %	6.8	14.3	0.001	0.010
Change of proportion of men with sedentary lifestyle, %	2.0	-6.1	0.033	0.017
Change of FINDRISC score, mean (95% CI)	0.73 (0.52, 0.93)	0.98 (0.57, 1.40)	0.230	0.414

[1] Statistical test (ANOVA or chi-squared test) for the difference between the groups of low risk men and elevated and high risk men.
[2] Statistical test (ANOVA or Logistic regression) adjusted for age.

As shown in Table 12, the elevated and high risk men who attended lifestyle interventions by a dietician and/or a diabetes nurse lost at least 5% weight more than twice as often as the non-attendees, and the difference between these groups was significant (age-adjusted p=0.038). Furthermore, the proportion of men with sedentary lifestyles decreased significantly among those elevated or high risk men who attended lifestyle interventions compared to the non-attendees (age-adjusted p=0.013). The FINDRISC score increased less among those elevated or high risk men who attended interventions compared to the non-attendees (age-adjusted p=0.033).

Table 12. Weight change, weight change of 5% or more, change of sedentary lifestyle and FINDRISC score during follow-up among the elevated and high risk men (FINDRISC ≥ 10, IFG or IGT) according to attendance at counselling sessions by a dietician and/or a diabetes nurse.

	No attendance at counselling (n=97)	**Attendance at counselling at least once** (n=141)	p-value[1]	p-value[2]
Weight change (kg), mean (95% CI)	0.3 (-0.10, 0.38)	0.01 (-0.87, 0.88)	0.594	0.414
Weight loss 5 % or more, proportion of elevated risk men, %	8.2	18.4	0.031	0.038
Change of proportion of men with sedentary lifestyle, %	-1.3	-9.4	0.021	0.013
Change of FINDRISC score, mean (95% CI)	1.5 (0.08, 1.15)	0.6 (0.86, 2.15)	0.037	0.033

[1] Statistical test (ANOVA or chi-squared test) for the difference between the groups of elevated plus high risk men with no attendance and at least one attendance at lifestyle counselling by a dietician and/or a diabetes nurse.
[2] Statistical test (ANOVA or Logistic regression) adjusted for age.

Among the elevated and high risk women the attendance at lifestyle counselling by a dietician and/or diabetes nurse did not significantly improve the risk factors compared to non-attendees.

5.5.2 Effect of lifestyle intervention on CVD risk factors and risk for T2D in working time groups

Both men and women in day work, non-flight shift work, and in-flight shift work gained weight and FINDRISC score, as well as, most of the studied CVD risk factors increased during the follow-up.

Among those 141 elevated and high risk men who attended lifestyle counselling by a dietician and/or a diabetes nurse, day workers' (n=67) total cholesterol decreased (-0.19 [95% CI -0.37, -0.00] mmol/l) compared to the increase among non-flight shift workers (n=64) (0.05[95% CI -0.12, 0.22] mmol/l) and in-flight shift workers (n=10) (0.45 [95% CI -0.07, 0.97] mmol/l). The difference between the working time groups was significant (p=0.015, age-adjusted p=0.024) and further adjustment for lipid-lowering medication did not influence the results. In addition, among the elevated and high risk men who attended counselling, day workers lost weight (-0.8 [95% CI -1.9, 0.3] kg) compared to the non-flight shift workers who gained weight (1.0 [95% CI -0.4, 2.4] kg). The difference between the working time groups in weight change was significant (p= 0.043) but the age-adjustment diluted the significance (p=0.095). The same trend was seen in BMI, which decreased among the day workers (-0.3 [95% CI -0.6, 0.1]) but increased among the non-flight shift workers (0.3 [95% CI -0.1, 0.8]) (p=0.037, age-adjusted p=0.085).

Among the elevated and high risk women, non-flight shift workers (n=28) gained some benefit from counselling by a dietician and/or diabetes nurse, their fasting glucose increased less (0.16 [95% CI -0.02, 0.34] mmol/l) compared to the day workers (n=37) (0.45 [95% CI 0.30, 0.61] mmol/l), (p=0.014, age-adjusted p=0.016).

6 Discussion

6.1 Main findings

Findings from the cross-sectional health check-up sub-data (Study II) suggest that metabolic syndrome is more prevalent among former male shift workers than current male day workers who have never worked shifts.

The results of the shift system change study carried out in the line maintenance unit among male participants (Study III) indicate that a faster speed together with a change from backward to forward direction in shift rotation alleviates daytime sleepiness. In addition, the study suggests that combinations of individual flexibility with company-based flexibility in a shift system may have favourable effects on shift workers' blood pressures.

The results from the cross-sectional sub-data of the health check-up study (Study IV) made up of men support our earlier findings that a rapidly forward rotating shift system is more age-friendly for sleep compared to backward and slower rotating three-shift systems. Quickly forward rotation shift workers considered their working time as less harmful to sleep and wakefulness compared with slower backward rotation shift workers. Older workers had less sleep complaints than their younger colleagues in the quickly forward rotating three-shift system. The age-differences in the inflammatory markers in the longitudinal data of the study partly depended on the shift system.

The renewed health check-up process, presented in Study I, effectively identified those employees with increased T2D and CVD risk who would benefit from lifestyle intervention. The use of the FINDRISC questionnaire is a feasible first-step screening method in occupational health care settings. The follow-up data of the health check-up study (Study V) showed that low intensity lifestyle interventions are feasible in occupational health-care settings. However, health benefits were observed only among men with increased risk.

6.2 Shift work and cardiovascular risk factors

6.2.1 Metabolic syndrome

The results of Study II suggest that former male shift workers' risk for metabolic syndrome can remain even after they have changed from shift work to day work. Compared to men, the risk for MetS among former female shift workers was lower and non-significant.

The risk of MetS among ex-shift workers has not been studied. Earlier research has analysed the association between current shift workers with or without night shifts and MetS, and positive associations have been found among both genders in cross-sectional studies (Kawabe et al. 2014; Lajoie et al. 2015; Sookoian et al. 2007; Ye et al. 2013) and in longitudinal cohort studies (Y. C. Lin et al. 2009; Pietroiusti et al. 2010), some studies suggest that the risk increases with years in shift work (De Bacquer et al. 2009; Guo et al. 2015). Canuto et al. could not establish any relationship between shift work and MetS in their review (Canuto et al. 2013), but Esquirol et al. found a link between shift work and MetS (Esquirol et al. 2011), and the recent review of Wang et al. supports a dose-response relationship between night shift work and MetS (F. Wang et al. 2014).

Unlike some earlier cross-sectional studies (Esquirol et al. 2009; Sookoian et al. 2007) and the above mentioned review (F. Wang et al. 2014), we did not find a significant correlation between night-shift work and having MetS. The majority of the night-shift workers in our cohort were aircraft maintenance workers, an occupational group which has adopted ergonomic shift systems in the company. In addition to our shift system change study (Study III), also another intervention study conducted among male workers of the same line maintenance unit (Harma, Hakola, et al. 2006) showed that the level of some health indicators, sleep, alertness, general health, and wellbeing at work improved in this occupational group. Thus it may be possible that both the systematic health screening of shift workers, as well as the implementation of ergonomic and flexible shift systems have influenced the risks in the present sample of night-shift workers.

The reason for the gender disparity in occurrence of the MetS in our study is not evident but may reflect a general gender difference in the health check-up study. Working conditions and different types of shifts probably have influenced the results in addition to private life (family) and health reasons, why former male and female shift workers have moved to day work. We had no data on these individual reasons for moving to day work.

In-flight workers showed no signs of an increased risk for MetS compared to day workers. In comparison to the other non-day work groups, they had higher educational levels and better health behaviour. Socioeconomic status strongly and inversely associates with several health outcomes including CVD risk (Kilander et al. 2001; Schumann et al. 2011; Siren et al. 2014). Also the strict aero-medical regulations with frequent health checks more than likely influence their health. In a retrospective cross-sectional study, Houston et al. compared the prevalence of CVD risk factors (age, body mass index, overweight and obesity, current smoking status, hypertension, and diabetes) among commercial aircrew and the UK general population (14,379 subject records). Even when comparisons were made with the highest income quintile of the general population to control for socio-economic status, pilots had a significantly lower prevalence of obesity and smoking. The authors concluded this reflects a healthy worker effect (Houston et al. 2011). Our findings from the cross-sectional data of the health check-up study (Study I) are in line with this observation. The MetS prevalence among all participants at the baseline was 34.1% in men and 17.4% in women, and among in-flight participants 30.5% in men and 12.3% in women. Among the Finnish population these percentages are 38.8% and 22.2%, respectively (Ilanne-Parikka et al. 2004).

6.2.2 Type 2 diabetes and other CVD risk factors

Diabetes and other disturbances of glucose metabolism are rare among Finnair's employees compared to the general Finnish population. In the age groups of 45-54 and 55-64 years, the prevalence of study detected T2D was 2.3% and 3.4% among men and 0.6% and 2.0% among women, in Finnair. In the general Finnish population, the corresponding numbers of prevalence for men are 5.9% and 8.7% and for women 2.5% and 8.0%, respectively (Saaristo et al. 2008). In the same age groups the prevalence of dysglycaemia were 19.1% and 20.9% for men and 6.7% and 9.2% for women, in Finnair, and the corresponding values in the Finnish population are 26.4% and 44.3% for men and 20.5% and 31.7% for women, respectively (Saaristo et al. 2008). The healthy worker effect and the preventive work of the health care services of the company probably account for some of these differences.

The baseline results of the health check-up study (Study I) revealed that the risk factor profiles linked to different working hours were not self-evident. The observed differences in CVD risk factors were minor between regular day workers and non-flight shift workers. However, the categories "regular day workers" and "non-flight shift workers" are heterogenic. Based on the findings of Study II, some of the regular day workers are ex-shift workers, who probably for health reasons had changed from shift work to day work. In addition, in spite of irregular working hours including night work and flights across time zones, the risk profile of the in-flight workers stood out from the rest. The occupational selection, the health standards for aviation occupations, and the regular health examinations controlled by the aviation authorities probably influenced the observed findings. Evidently, too, the health risks related to shift work can be attenuated by lifestyle choices as the in-flight workers were the most educated and they had the best lifestyle habits.

6.3 Prevention

6.3.1 Effects of the shift system changes

Sleep and alertness

The shift system change study (Study III) indicated that a faster speed, together with a change to the forward direction in shift rotation, alleviates daytime sleepiness among male maintenance workers. This beneficial effect of a rapidly forward-rotating shift system on workers' alertness is consistent with the findings of some earlier reports (De Valck et al. 2007; Hakola and Harma 2001; Harma, Hakola, et al. 2006). The declining trends in the ESS score and caffeine consumption in this group were congruent with a decrease in daytime sleepiness. The reduction of days with significant sleepiness by about 1 day a week, observed in this study, is probably clinically important. The beneficial effect of the rapidly forward rotating shift system on sleep was also seen in the cross-sectional sub-data of the health check-up study (Study IV). Shift work compared to day work was, in general, associated with problems to fall asleep and feelings that working times were harmful to sleep and wakefulness, but shift workers who worked in the forward rotating shift system considered their working times to be less harmful compared to those who worked in the backward rotating shift systems.

The change from a rather slow backward-rotating shift system to a very rapidly forward-rotating shift system consisted of changes both in the number of consecutive morning, evening, and night shifts (from three to one) and in the direction of the rotation (from backwards to forwards), as well as of some minor changes in the starting and ending times of the shifts. However, the number of successive shifts (three) and free-days (two) did not change. The observed results in the rapidly forward rotating shift system can probably not be connected to any single element of the shift schedule, merely to the combination of the simultaneous changes.

Age differences

The cross-sectional sub-data of the health check-up study (Study IV) suggested that a fast forward rotating shift schedule may alleviate and slowly backward rotating shift schedules may exacerbate sleeping problems among older shift workers. Age did not influence sleep in general, but older workers in the quickly forward rotating shift system had less sleep complaints than their younger colleagues in the same shift system. The beneficial effects of the forward-rotating shift system for older employees' sleep and health indicators are in line with earlier findings (Bonnefond et al. 2006; Hakola and Harma 2001; Harma, Hakola, et al. 2006; Klein Hesselink et al. 2010).

The shift system change study (Study III) was conducted in the same airline line maintenance unit as the study of Härmä et al. (Harma, Hakola, et al. 2006), which showed that although the rapidly forward rotating shift system (identical to that of our study) increased operating hours at night, it had positive effects on sleep, alertness and well-being, especially among the older shift workers. This finding is probably due to a slower circadian adaptation to night shifts and increased morningness preference of older workers (Harma et al. 1994). With only a single night shift, no delay in the circadian rhythms is necessary, and morningness or an inability to shift circadian rhythms during evening and night shifts supports the recovery of sleep–wakefulness during the following free days. The participants slept for a shorter period of time during the day after a single night shift, but longer and better during the recovery period between the single night and morning shifts (Harma, Hakola, et al. 2006). Because of these positive experiences gained by older shift workers from this earlier intervention study, a higher number of older persons selected the rapidly forward rotating shift system in the present shift system change study.

These studies can give no basis for the determination of the positive effects of the fast forward rotating shift system for older workers (e.g. whether it is due to the speed or the direction of the rotation). However, the research evidence supports the conclusion that a fast forward instead of the slower backward rotating shift systems causes less health problems among older workers (Harma 2006; Knauth and Hornberger 2003; Sallinen and Kecklund 2010). It has been argued that age-specific aspects should be considered in shift work planning (Blok and de Looze 2011; Costa 2003; Costa and Sartori 2007; Harma, Kompier, et al. 2006; Knauth and Hornberger 2003).

Cardiovascular risk factors

In the shift system change study (Study III) systolic blood pressure decreased and heart rate showed a declining trend among the workers in the flexible shift system when the 3-shift systems were compared (Figures 4a and 4b). A decrease of 10 or even 2 mm Hg in systolic blood pressure has been associated with a marked reduction in the risk of stroke and mortality from ischemic heart disease (Lawes et al. 2004; Lewington et al. 2002). The observed 6 mm Hg decrease of systolic blood pressure, if long-lasting, may thus have a beneficial impact on shift workers’ health.

In our study, the change from the slowly backward rotating shift system to the rapidly forward rotating shift system did not result in significant changes in the studied cardiovascular risk factors. There are only a few studies that have evaluated the effect of the change of shift schedule on CVD risk factors. In the earlier mentioned small short-term study (Orth-Gomer 1983), serum levels of triglycerides and glucose, systolic blood pressure and the urinary excretion of catecholamines decreased after a 4-week period of clockwise, as compared with counter-clockwise shift rotation. Another small experimental 3-week follow-up study found no difference in salivary cortisol levels between a fast-forward and a slow-backward rotating shift systems (De Valck et al. 2007). Vangelova using a random controlled design, compared a very fast forward rotating shift system to a very fast backward rotating shift system and found higher salivary cortisol values during the morning and night shifts, as well as worse quality of sleep among workers in the fast backward rotating shift system probably indicating insufficient recovery (Vangelova 2008).

There is also a lack of research on the effects of flexible shift systems on psychophysiological reactions. The results of our study suggest that combining individual elements of work time control with company-based variability in a shift system can have favourable effects on shift workers' cardiovascular health. The decrease in systolic blood pressure in combination with a declining trend in heart rate probably indicates a decrease in psychophysiological stress in the more flexible shift system. Unfortunately, the questionnaire used in this study did not include items on workers' opinions of work stress and opportunities to influence their workhours. In the flexible shift system, the actual time-off period from the end of the last morning shift to the beginning of the first night shift also varied over a wider range (from 52.5 to 80.5 hours) than in the other two shift systems. It is thus possible that the improvement in markers of cardiovascular stress could also be explained by the longer recovery time between the separate shift sequences in this shift system.

Apart from the positive changes in blood pressure and heart rate in the flexible shift system, neither other cardiovascular risk factors (BMI, blood lipids, and glycaemic control measured by HbA1c and fasting glucose) nor dietary and lifestyle factors improved in the shift system change study. The follow-up time of 7 to 8 months was probably too short. Also the relatively small sample size may have decreased the statistical power. However, in the sub-data of the health check-up study (Study IV) leukocyte counts, a biomarker of inflammation, seemed to decrease during the 2.5-year follow-up time as the 3-shift workers changed from the backward rotating shift systems to the rapidly forward rotating shift system (Figure 7).

The employer benefited from the changed shift systems in increased working time in the rapidly forward rotating shift system and in company control and decision latitude in the flexible shift system. Because the results of the shift system change study were beneficial for both the employer and employees, as well as the positive experiences from the earlier intervention study in the same work place (Harma, Hakola, et al. 2006), these new shift systems have been implemented in the line maintenance unit of the airline.

6.3.2 Lifestyle intervention

Feasibility of screening and lifestyle counselling along with the health check-up process

The new health check-up process described in detail in the original article of Study I proved to be feasible and well-accepted in our OHC setting. The extended health check-up successfully identified groups of employees that would benefit from lifestyle intervention. The protocol of screening and referring individuals with elevated diabetes risk to lifestyle counselling (Figure 1. in the original article of Study I) is in congruence with the European IMAGE guideline for diabetes prevention (Paulweber et al. 2010). The FINDRISC score seems to be a feasible screening method as it makes it possible to identify simultaneously employees with cardiovascular and diabetes risks.

Effectiveness of the low-intensity lifestyle intervention along with health check-up

Compared with the more intensive intervention trials, such as the Finnish Diabetes Prevention Study (Lindstrom, Ilanne-Parikka, et al. 2006; J. Tuomilehto et al. 2001) the effect on risk for T2D and CVD was modest in our health check-up study (Study V). However, the DPS was an “efficacy study” and our renewed health check-up project was a pragmatic “effectiveness study” (Singal et al. 2014), which was implemented by the occupational health care service as part of its normal work. Accordingly, the intervention intensity and delivery had to be adjusted to fit in with working practices.

The modest results of our “real life” health check-up study may also be due to the more favourable baseline risk profile of the participants, leaving less room for improvement. Finnair’s employees, particularly women, were slightly leaner (mean BMI 26.9 for men and 24.4 for women) than the general Finnish population (in 2007, mean BMI 27.2 and 26.5 for men and women, respectively) (Vartiainen et al. 2010). Diabetes and other disturbances of glucose metabolism were also rare among Finnair’s employees compared to the general Finnish population (page 83, section 6.2.2). Lifestyle interventions targeted at lower risk individuals have had only minor effect on diabetes risk, e.g. in a Dutch study (FINDRISC score $\geq$13) weight loss and glucose decrease were non-significant between the intervention and control groups at 2.5 years (Vermunt et al. 2012). In a non-controlled mixed method pilot study (FINDRISC ≥ 11) the results were better. At a 12-month follow-up weight and waist circumference decreased and physical activity increased significantly (Penn et al. 2013). Probably motivation for changing their lifestyles among lower risk persons is not very high, thus partly explaining the modest results of the voluntary interventions offered in our health check-up study (FINDRISC ≥ 10).

The challenges of stressful shift work on making lifestyle changes may play a role, too. Initially, we aimed to have the group intervention as the core intervention mode, to increase the number of contacts between the counsellor and the client in a cost-effective way. Unfortunately, shift work proved to be an obstacle to participation, and after the first year group sessions were not offered. A recent Danish study (31% shift workers, of whom 38% night shift workers) could not confirm that shift workers in general report a lower availability of and participation in workplace health promotion compared to day workers (Nabe-Nielsen et al. 2015). However, group activities or organized events are often inflexible and do not meet the needs of shift workers with the most irregular working times, and this may result in these workers not participating in these particular activities.

In a systematic review of the evidence for an effect of lifestyle-targeted interventions at the workplace on the main biological risk factors for cardiovascular disease, the authors concluded that interventions were profitable when targeted at populations with elevated risk for CVD (Groeneveld et al. 2010). Dunkley et al examined the effectiveness of diabetes prevention programmes in real world settings and whether adherence to international guideline recommendations is associated with effectiveness. The evidence of their systematic review and meta-analysis suggested that pragmatic diabetes prevention programmes were effective and adherence to the guideline recommendations on intervention content and delivery was associated with a greater weight loss at a 12-month follow-up (Dunkley et al. 2014). Also in our study, significant health benefits were observed among men with elevated and high diabetes risk who participated in the counselling sessions with a dietician and diabetes nurse. Probably, one important reason for the modest results of our study was the low intervention intensity with an average number of counselling sessions of 1.6 compared, for instance, with 7 sessions in the DPS during the first year only. The participation or compliance in lifestyle counselling by a dietician or a diabetes nurse was relatively high (61%) but the adherence was low (only 24% of the participants in the elevated risk group and 36% of those in the high risk group attended more than once) and far too many (46%) of the high risk individuals did not attend counselling at all (Table 10).

Characteristics associating with participation in lifestyle interventions

In general, little is known about what characteristics of individuals at risk are associated with participation in lifestyle interventions. In our health check-up study, there was no gender difference in the participation in lifestyle counselling given by a dietitian or a diabetes nurse, which is encouraging, as men are usually considered a challenging target group for lifestyle interventions (Dryden et al. 2012). Higher baseline FINDRISC scores and the presence of clinical and lifestyle risk factors as well as problems in sleep and mood increased attendance in lifestyle counselling sessions. The factors associating with participation differed between genders in some aspects, which may be a result of the different requirements and challenges of work and health. Men worked mainly in blue collar tasks, e.g. in technical, ground or cargo services, and women mainly in white collar duties, e.g. in office or gate services and in-flight duties. Among the men, years in shift work increased participation in intervention, but this did not affect participation among women. Older age among men and sleeping problems among women as well as sedentary lifestyle among both genders correlated with participation in lifestyle interventions. These are factors that are related to the increased risk of type 2 diabetes and cardiovascular disease, thus indicating that we were indeed identifying and making interventions for the right target group.

6.4 Methodological considerations

The longitudinal research framework with data from clinical measurements, biological tests, and the wide ranging questionnaires are strengths of this series of studies. Also retrospective data of exposure to shift work was utilized in the metabolic syndrome cross-sectional study (Study II). The research framework including interventions both on work and workers and focusing on prevention completes the cohort results and increases the study relevance. The commitment of the organizations to the research programme has been high and the results of these studies have been utilized in the airline. The new rapidly forward and flexible shift systems have been implemented in the line maintenance service of the company, and the new health check-up process has become a normal practice in Finnair Health Services.

6.4.1 Study populations and participation in the studies

All participants in this series of studies were employed by one company. However, the variety of included occupations, diversity of working times, large sample sizes, and equal gender distribution make the target group of the health check-up study (Studies I, V and the sub data of Study II) representative and the results could be generalized to other occupational health care settings. On the other hand, the participants in Studies III and IV were recruited from two partially overlapping samples of men in the line maintenance units of the company. So the results of these studies may have limited generalizability to e.g. women and white collar workers.

The attendance at the health check-up was compulsory only for in-flight workers. However, participation in the health check-up study was voluntary for all. We did not have the ethical permission to use the information of the employees who attended the health check-up but refused to participate in the study. The slightly differing participation rates of regular day workers and non-flight shift workers probably arose from the fact that it was easier for day workers to attend the health check-ups which were carried out during normal office hours. The overall participation rates in the health check-up (66% of the target group) and in the health check-up study (84% of those who attended the health check-up) were, however, relative high and comparable to other voluntary health checks in Finnair and e.g. to another Finnish OHC study (Taimela et al. 2008), as well as to Finnish population screenings (Vartiainen et al. 2010).

The interest to participate in voluntary health check-ups may be lower for people who feel that they are healthy. The participation rate in the follow-up of the health check-up study revealed that non-participants were younger and their FINDRISC scores were lower in agreement with this theory. Most drop-outs in the follow-up of the health check-up study occurred among female in-flight workers. Being the healthiest group at baseline they perhaps did not find the additional voluntary health check process to be as necessary as others. Somewhat surprisingly, men participated more eagerly than women and also benefitted from the health check-up and lifestyle interventions more than women. An explanation for this may be that in the airline company men are used to attending statutory health checks because of the possibility of work related exposure such as chemical or physical factors and this may have influenced their attitudes towards health surveys and participation.

In general, the participation rate in the follow-up study was lower than expected, and this may have weakened the results with relation to intervention between genders and working time groups.

6.4.2 Selection

Health selection in working time groups and the healthy worker effect may have influenced some of our results. We had no data on individual’s reasons for moving from shift to day work. According to the healthy worker effect, those who stay in shift work are survivors who are healthy or able to cope with strenuous shift work, and those who move to day work are likely to have a worse health status or are impacted negatively by shift work and remaining a shift worker would be untenable for them. Thus, the healthy worker effect may result in an under, rather than overestimation of the effects of shift work. Kivimäki and co-workers reported that employees with cardiovascular risk factors were more likely to leave an organization regardless of the type of work schedule. They concluded that health-related selection out of shift work is not a major source of bias in shift work and CVD studies (Kivimaki et al. 2006). This is probably the case when employees do not have possibilities to move to day work in the same organization. However, the occupational health service of the airline systematically screens the health of employees and, as supported also by Finnish law, the possibilities to move to less strenuous shift work schedules or to day work have been rather good in the company, except for in-flight workers who, on the other hand, are most committed to their work. The costs to the employee usually are limited to reduced salary. This selection out of shift work can bias the results of shift work and cardiovascular risk factors when a high number of former shift workers are included in a group of day workers.

The fast forward rotating 3-shift system became popular among the older workers in the line maintenance of the airline company, when its beneficial effects on sleep and cognitive functions were first reported (Harma, Hakola, et al. 2006). The occupational health service of the company also has supported transfers to this new shift system based on individual health and sleep reasons. Thus it is probable that the forward rotating shift system includes more workers with poorer tolerance to shift work. This selection bias may have resulted in diminished favourable effects of the forward rotating shift system in relation to the health of the older workers, diluting some of our results in Studies III and IV.

6.4.3 FINDRISC score

The FINDRISC diabetes risk score was originally developed to identify individuals with increased risk for T2D, but it has proven to be a valid predictor for coronary heart disease, stroke, and total mortality, too (Silventoinen et al. 2005). In our study, metabolic syndrome and other studied CVD risk factors correlated well with FINDRISC scores (Table 9). Therefore, in evaluation of the risks for both T2D and CVD in parallel the FINDRISC seems to be a feasible, low-cost, non-invasive first-step screening method.

It has been argued that the FINDRISC score is probably not an optimal method for evaluating changes in diabetes risk in repeated surveys as most of the questions are either non-changeable (like family history of diabetes) or only change for the worse (like age). It is probably not common that people would deliberately change their answers for the FINDRISC (claiming e.g. that they eat fruit and vegetables daily when they do not) to comply with the advice. The practice effect at play is probably quite small in our health check-up study because of the long interval of the two FINDRISC enquiries (from 1.4 to 4 years). Optimally, the test result should be checked and interpreted by a health-care professional.

6.4.4 Size of effects

The significance of the effect size can be explored from different perspectives e.g. from statistical significance, clinical relevance, public health or cost effective points of view. The size of the effects from the interventions on individual level was quite small in our studies. However, on the population level even minor positive changes may be clinically significant; e.g. only modest reductions of cholesterol levels may reduce the CVD risk to a tangible degree in the long run (Law et al. 1994). In addition, as the leading CVD risk factor is raised blood pressure to which 13 per cent of global deaths is attributed ("World Heart Federation " 2012), and as a decrease of even 2 mm Hg in systolic blood pressure has been associated with a reduction in CVD risk (Lawes et al. 2004; Lewington et al. 2002), the 6 mm Hg decrease of systolic blood pressure observed in our shift system change study may have a beneficial impact on shift workers’ health. It is noteworthy, too, that one percent weight loss corresponded to 10% higher odds for MetS resolution in a clinical trial (Ilanne-Parikka 2011), so the slight weight reduction in our health check-up study among elevated and high risk men may also be beneficial.

6.4.5 Shift specific questions

With the sub-data of the health check-up study (Study IV), we explored the age-dependent association of shift systems with sleep-wakefulness. The differences between the shift systems were modest when we used general questions on sleep and sleepiness e.g. ESS and questions on sleep length, difficulties to fall asleep, awakenings during sleep, and day time fatigue during the past three months. Härmä et al. used similar questions about sleep and sleepiness and found a greater amount of sleep disturbances among male 2-shift, 3-shift and irregular shift workers in comparison with day workers (Harma et al. 1998). However, general questionnaires, such as the ESS, have not revealed significant differences concerning sleepiness between shift workers and day workers in many of the earlier studies (Garbarino et al. 2002; Halvani et al. 2009). It is probable that the use of shift-specific questions such as asking directly, for example, the length of day sleep after a night shift, would have resulted in larger differences between the different shift systems. In an earlier study conducted in the same work site as the present study, shift-specific questions revealed clear differences in sleep length, sleep quality and subjective sleepiness between the morning, evening and night shifts (Bonnefond et al. 2006).

6.4.6 Exposure assessment

The issue of the exposure assessment in shift work research has recently been highlighted by Härmä et al. (Harma et al. 2015). In epidemiological studies the exposure is usually assessed by questionnaires. The reliance of self-reported exposure data is a typical limitation of shift work studies. Such data is likely to produce unreliable estimates due to recall bias, difficulties to adequately sum up how many night shifts one has worked in a month in a varying shift schedule, and to the respondents' interpretation of the meaning of 'worked nights'. In high-quality epidemiologic studies objective individualized duty hour data retrieved from employers' worktime register are important to reliably assess the exposure (Harma et al. 2015). In our shift system change study, it was possible to describe the studied shift systems (rapidly and slowly rotating shift system, flexible shift system) in great detail from the information available from the employer. However, in the health check-up study, working time was assessed by questionnaires and thus probably the information was more unsound.

6.5 Practical implications

Occupational health care, encompassing the vast majority of the Finnish workforce, is an important part of the primary health service system and welfare policy in Finland. Because shift work, especially night shift work, induces sleep loss and circadian disruption with resulting adverse metabolic and cardiovascular consequences, regular health checks for night shift workers are statutory in Finland ("Guide for Application of the Occupational Health Care Act " 2004). Screening shift workers' health regularly, informing employees about the health risks of shift work, and offering them lifestyle counselling to counteract the avoidable risks are part of the essential preventive work of OHC. In addition, evaluating and suggesting methods to enhance working conditions, especially working times in shift work, are part of traditional preventive OHC work.

In a 24/7 society the option to eradicate shift working is not realistic. Therefore, shift workers' increased risk of CVD requires the efforts of OHC for health promotion and early identification of individuals at risk. Our results suggest that former shift workers have an increased risk of MetS and this should be recognized in occupational health care and taken into account in preventive work. Some modifications to shift work itself are also feasible. Our studies indicate that a faster speed, together with a change to the forward direction, in shift rotation have positive effects on sleep and wakefulness. In addition, combining individual flexibility with company-based flexibility in a shift system may have favourable effects on shift workers' cardiovascular health. Our findings concerning different shift systems and age have practical importance: as our workforce is ageing, age specific aspects should be considered in the design of new shift systems. In workplaces with varying shift systems the possibility of elderly employees with health problems to change to a more "age-friendly" shift schedule would enhance older workers' well-being and help them to better cope with shift work.

Our health check-up study revealed that interest in attending lifestyle counselling given by a dietician and/or a diabetes nurse was relatively high among individuals with elevated and high diabetes risk who probably benefit most from counselling. However, the intensity of participation was low, and most individuals only attended a single counselling session. Also, combining irregular working times and group counselling turned out to be challenging. Based on the health check-up study we suggest that lifestyle interventions should be targeted at risk individuals and interventions would benefit from new and innovative means. They should be more intensive and better integrated into the occupational health procedures, and should be done by a multi-professional team and possibly be complemented by the application of modern interactive E-health technologies. More comprehensive interventions tackling material, organizational and work-time related conditions simultaneously may be most successful (Montano et al BMC20014).

7. Summary and conclusions

This thesis explored the association of former and present shift work with CVD risk factors and the risk of T2D and tested two kinds of intervention, shift system change and lifestyle counselling, to improve shift workers' cardiovascular health and their abilities to cope with diverse working times along with ageing. There is shortage of occupational research evaluating both of these aspects of the preventive work. This thesis concentrates on these issues offering ideas for practice.

Shift work is a specific risk factor for metabolic disorders and cardiovascular diseases. This is the first study to explore how various non-day work schedules and previous exposure to shift work are associated with metabolic syndrome. The results suggest that former male shift workers have an increased risk of MetS and it should be recognized in occupational health care and taken into account in the preventive work of OHC.

The shift system change study indicated that a faster speed of rotation, together with a change to a forward direction in shift rotation alleviates daytime sleepiness. The sub-data of the health check-up study confirmed this finding among older male shift workers. In addition, combining individual elements with company-based flexibility in a shift system probably induce favourable effects on the psychophysiological stress shift workers experience, this was deduced from decreased blood pressure values and a decreasing trend in heart rates in our shift system change study. Shift work disturbs bodily circadian rhythms and sleep. As ageing is related to slower circadian adaptation to consecutive night shifts and increasing problems to sleep during the day, coping with shift work become more difficult for older workers, especially in slower rotating shift systems. Thus, age-specific issues should be taken into account in shift planning.

The extended health check-up process proved to be effective in identifying workers with an increased risk of type 2 diabetes and other CVD risk factors. Metabolic syndrome and other studied CVD risk factors correlated well with the FINDRISC score. Therefore, evaluation of the risks for both T2D and CVD in parallel is warranted, and in this the simple questionnaire, FINDRISC score seems to be a feasible, low-cost, non-invasive first-step screening method. Optimally, the test result should be checked and interpreted by a health-care professional.

The implementation of a low-intensity lifestyle intervention along with a health check was feasible in our occupational setting. We found no positive effect on the health of low diabetes risk employees, who were not offered additional lifestyle intervention. However, elevated risk individuals, especially men, gained some health benefit from lifestyle counselling offered by a dietician and/or a diabetes nurse. All in all, the results achieved are encouraging as the participants of our “real life” health check-up study were mostly relative low risk individuals due to occupational selection and healthy worker effect, thus leaving less room for improvements. Focusing on high risk individuals and intensifying the interventions would have been more advantageous.

Most of the Finnair employees are shift workers working on aviation duties with a requirement for good health and high vigilance. The Finnish development strategy for OHC outlines measures for promoting employees’ health and working capacities. WHO has estimated that with adequate changes in lifestyle over three-quarters of all CVD mortality may be prevented. Although some of the effects of shift work are probably unavoidable, the effect of disruption of circadian rhythms can be ameliorated by the careful management of shifts. As the workforce is ageing, the age specific aspects should be considered in the design of new shift systems. The present study, which includes interventions focusing on both working times and workers’ lifestyle serves both the national health strategy and the airline’s health policy. The new shift systems and the renewed health check-up process have been implemented in the airline. The future challenge will be increasing compliance with and adherence to voluntary health checks and focusing interventions especially on high risk individuals and also ex-shift workers. It is important to identify the work and individual related characteristics affecting intervention project attendance to develop more effective methods for chronic disease prevention in OHC.

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