Review of the epidemiologic evidence concerning a causal relation between night shift work and ischemic heart disease

Poul Frost, Henrik Albert Kolstad, Jens Peter Bonde

Correspondence to:

Poul Frost

Department of Occupational Medicine

Århus University Hospital,

Noerrebrogade 44, Building 2C

8000 Århus C

Phone: (+45) 89494290

E-mail: pfros@as.aaa.dk

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Foreword

This review was undertaken on request by the Danish National Board of Industrial Injuries. The Board wanted a review of the epidemiologic evidence for a causal association between nightwork and ischemic heart disease. The review follows the guidelines of the Scientific Committee of the Danish Society of Occupational and Environmental Health for establishing a reference document on the causal relation between an occupational exposure and a disease outcome. The review focuses on epidemiologic studies of shift work and ischemic heart disease. Other relevant literature concerning the relation between engagement in shift work and alteration in cardiovascular risk factors are included, but a comprehensive review of this literature was beyond the scope of this study.

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Poul Frost, MD, PhD

Dansk resume

Gennemgang af den epidemiologiske dokumentation for årsagssammenhæng mellem natarbejde og iskæmisk hjertesygdom.

Skifteholdsarbejde, specielt hvis dette involverer arbejde i nattetimerne, kan tænkes at øge risikoen for iskæmisk hjertesygdom. Mulige mekanismer bag dette kan være negativ påvirkning af traditionelle risikofaktorer som blodlipider og blodtryk, ændring af livsstil med øget rygning og manglende motion, og måske psykosociale påvirkninger pga. vanskeligheder med at kunne indgå i sædvanlige sociale sammenhænge.

Iskæmisk hjertesygdom omfatter forskellige forstyrrelser i hjertemusklen forårsaget af iltmangel. Dette skyldes oftest forkalkning af kranspulsårerne, men kan også skyldes andre forhold. De mest almindelige iskæmiske hjertesygdomme omfatter hjerte- eller brystkrampe og blodprop i hjertet. I Danmark døde 9.111 personer af sygdommen i 2000, heraf godt 70 % efter 75 års alderen. Dødeligheden på grund af iskæmisk hjertesygdom er faldet med mere end 50 % blandt 34-75-årige siden 1990. I 2002 var der 24.434 førstegangs indlæggelser i Danmark på grund af iskæmisk hjertesygdom, hvoraf 9.736 var pga. hjertekrampe, 8.919 pga. blodprop i hjertet og 5.809 pga. anden iskæmisk hjertesygdom, som f.eks. kan være komplikationer i efterforløbet af en akut blodprop i hjertet, andre former for iskæmisk hjertesygdom eller kronisk iskæmisk hjertesygdom.

Tyve procent af den europæiske arbejdsstyrke oplyser, at de har natarbejde mindst en gang per måned. Ti procent har natarbejde mere end 5 nætter og lidt mindre end en halv procent har fast natarbejde.

Denne gennemgang, som er udarbejdet i henhold til retningslinjer fra den Videnskabelige Komite under Dansk Selskab for Arbejds- og miljømedicin, resumerer og diskuterer epidemiologiske studier, hvor der er oplysninger om, at deltagere har arbejdet om natten eller på skiftehold, og som i relation her til har vurderet risikoen for at udvikle iskæmisk hjertesygdom. I alt 918 artikler blev vurderet, hvoraf 16 opfyldte kriterierne for inklusion. Hver enkelt af de inkluderede studier gennemgås i rapporten med hensyn til metoder, centrale fund, styrker og svagheder. Der gives en samlet oversigt over resultaterne på tværs af studierne og den samlede dokumentation for en årsagssammenhæng vurderes.

Af de 16 undersøgelser brugte to meget brede sygdomskriterier, sådan at disse ikke bidrog til den samlede dokumentation. Af de 14 studier tog fem udgangspunkt i den almene befolkning, mens ni tog udgangspunkt i bestemte arbejdspladser eller i bestemte fag. Da kun to studier inkluderede kvinder, var det ikke muligt nærmere at vurdere en eventuel. kønsforskel i risiko.

Otte studier undersøgte sammenhængen mellem natarbejde og død på grund af iskæmisk hjertesygdom (mortalitetsstudier), blandt hvilke et studie viste statistisk signifikant forøget risiko. Dette studie havde begrænsninger med hensyn til eksponeringsmåling og studiestørrelse. I de syv øvrige mortalitetsstudier var der ikke sikker forskel i dødelighed. Estimaterne af den relative risiko lå her mellem 0,64 og

1,19. Da der kan være nogen usikkerhed forbundet med at fastslå dødsårsager specielt i ældre aldersgrupper, er der dog mulighed for, at resultaterne i disse studier kan undervurdere en evt. sand risikoforøgelse.

Syv studier undersøgte sammenhængen mellem skifteholdsarbejde og sygdom eller død på grund af iskæmisk hjertesygdom (incidensstudier). Seks af disse fandt øget relativ risiko, i fem studier til omkring 1,3 og i et studie til ca. 2, mens et studie ikke fandt nogen risikoforøgelse. I tre af disse studier var estimatet statistisk signifikant. Utilstrækkelig eller begrænset kontrol af andre vigtige risikofaktorer, brug af selvrapportering af eksponering specielt i studier, der indhentede historiske oplysninger om skifteholdsarbejde og mulighed for overrepræsentation (selvselektion ind i studier) af syge relateret til eksponering, kan i forskelligt omfang have bidraget til en overvurdering af risikoen, mens upræcis eksponeringsmåling i et i øvrigt velgennemført studie gav mulighed for, at risikoen kunne være undervurderet i dette.

Det var karakteristisk for de fleste studier, at oplysninger om arbejdstid havde begrænset detaljering med hensyn til eksakt placering på døgnet og med hensyn til det samlede omfang af natarbejdet. Nogle studier baserede eksponeringsmåling på detaljerede registreringer af studiedeltagernes arbejdstid indhentet fra virksomhederne, men der var alligevel begrænsninger med hensyn til at kvantificere og typebestemme skifteholdsarbejdet. Det er indtrykket fra de fleste studier, at deltagere med nat/skifteholdsarbejde havde dette som led i en arbejdstilrettelæggelse, der vekslede mellem dag, aften og nat, mens få arbejdede fast om natten. Enkelte studier kunne skelne mellem disse typer af natarbejde, men grundlaget for at vurdere, om der er en særlig risiko forbundet med den ene eller anden type af natarbejde, var

utilstrækkeligt. Risiko i relation til det samlede omfang af natarbejde (fast eller tilbagevendende) blev analyseret i fem studier. I to studier, der baserede sig på uafhængige eksponeringsoplysninger, så man ingen sikker tendens til stigende risiko, mens tre studier, der anvendte selvrapporterede oplysninger fandt en øget risiko efter henholdsvis 6, 10 og 30 år med natarbejde. Et af disse studier rapporterede desuden en mere end halveret risiko blandt deltagere med mere end 20 års udsættelse. Alt i alt er der således ikke god evidens for at risikoen for iskæmisk hjertesygdom stiger med omfanget af natarbejde. I den forbindelse manglede der studier, der formålsrettet indhentede mere deltaljerede eksponeringsoplysninger, sådan at risiko i relation til type og omfang af natarbejde kunne være undersøgt bedre.

Det har været en gennemgående diskussion, hvorvidt og hvordan andre risikofaktorer, især metaboliske (overvægt og kolesterolniveau) og rygevaner skal kontrolleres. Hvis en effekt af natarbejde går gennem ændringer i metaboliske forhold eller ændrede rygevaner, så vil kontrol af disse tendere til at sløre en effekt. Dette var dog ikke et problem i to studier, der ikke fandt øget dødelighed, da disse kontrollerede for andre risikofaktorer baseret på oplysninger indhentet før start på natarbejde. Kun enkelte studier i øvrigt oplyste resulter med og uden kontrol af andre risikofaktorer. Disse pegede ikke entydigt på problemer med overkontrol, selv om de øvrige risikofaktorer næppe blev målt før starten på natarbejde.

Der er på det seneste kommet undersøgelser, der peger i retning af større tendens til uhensigtsmæssige ændringer i metaboliske forhold og rygevaner blandt natarbejdere, men der er også undersøgelser, der tyder på, at rygere oftere end ikke-rygere starter i natarbejde. En nærmere afklaring af spørgsmålet om effektmediering gennem

ændrede metaboliske forhold og rygevaner og deres betydning for risikoen for iskæmisk hjertesygdom, vil kræve undersøgelser, der måler risikofaktorer før start på natarbejde og gentager disse målinger med passende mellemrum i løbet af studiet.

Sammenfattende fremtræder den foreliggende dokumentation delvis modstridende med hensyn til spørgsmålet om årsagssammenhæng mellem natarbejde og iskæmisk hjertesygdom. Resultater fra mortalitetsstudier taler overvejende imod en øget risiko, mens incidenstudier overvejende taler for en mindre øgning. Som ovenfor anført er der mulighed for, at forskellige fejlkilder kan have influeret på resultaterne, sådan at tolkningsmulighederne er begrænsede. Grundlaget for at vurdere risiko i relation til omfang og type af natarbejde samt evt. kønsforskel i risiko er utilstrækkeligt.
I henhold til kriterierne udarbejdet af Den Videnskabelig Komite under Dansk Selskab for Arbejds- og miljømedicin er det vores vurdering, at den samlede epidemiologiske evidens for en årsagssammenhæng mellem natarbejde og iskæmisk hjertesygdom må anses for begrænset (limited evidence of a causal association (+)).

Objective

To evaluate the epidemiologic evidence for a causal relation between nightwork and ischemic heart disease.

Background to the review

In 2007 the Danish Board of Industrial Injuries requested a review on the epidemiologic evidence for a causal relation between continual nightwork or working at night in rotating shifts and ischemic heart disease. The Board also requested that gender effects were considered.

Ischemic heart disease

Ischemic heart disease refers to a condition with diverse disturbance of cardiac function due to relative lack of oxygen in the myocardium. Most often this is caused by atherosclerosis in the coronary arteries. Reduction in myocardial perfusion can be limited from other causes such as thrombi, spasm and other more rare conditions[1].

The 10th revision of the International Classification of Diseases classifies ischemic heart disease into angina, myocardial infarction (or re-infarction) with or without complications, other acute ischemic heart diseases, and chronic ischemic heart disease.

Mortality by coronary heart disease is declining rapidly in European countries in most age groups. In Denmark, the age-standardised mortality rate has dropped with 53% among males and 43% among females for the 35-74 years age group in the period 1990 - 2000. In 2000, ischemic heart disease was registered as the cause of death in 9,111 cases in Denmark of which 72 % occurred after the age of 75[2].

Mortality from ischemic heart disease increases steeply with age. In 2000 the mortality rate in Denmark was 3.4/100,000 among those 35-39 years of age and 487/100,000 among those 70-74 years of age. In 2002, 24,464 persons were hospitalized for the first time due to ischemic heart disease of which 9,736 were due to angina, 8,919 to myocardial infarction and 5,809 to other ischemic heart diseases[2]. Socioeconomic status in both adulthood and childhood[3;4], gender, life style factors, including body mass index[5] and smoking, blood pressure and blood cholesterol[5] are well established risk factors for ischemic heart disease[6]. It is likely that population wide changes, especially in smoking habits, but also in blood lipids, and blood pressure, in favourable directions, have substantially contributed to the decline in ischemic heart disease seen in European countries[7-9].

Work at night and ischemic heart disease

Shift work has been suggested as a risk factor for ischemic heart disease[10-13].

In EU countries, about 20 % of employees and self employed work at least one night a month (at least 2 hours between 10 p.m. and 5 a.m.). Ten percent work 1-5 nights, ten percent more than 5 nights per month, and 0.4 % work permanent night shift. Nightwork is most prevalent in agriculture, hotels, restaurants, transport, and in health care[14;15]. A thorough presentation of possible causal mechanisms is given in a previous review[10]. These include mismatch of circadian rhythm, social disruption, and behavioural changes. A mismatch of circadian rhythm may have influence on nutritional factors related to timing of meals, lack of sleep, and stress related to sleep deprivation that could lead to unfavourable metabolic disturbances or a metabolic syndrome[16;17]. Working at night and sleeping in day time may disturb the social temporal pattern and lead to social isolation and stress. An unfavourable distribution

of behavioural factors like smoking, diet, and drinking could be influenced by shift work and thus be mediators of an effect of shift work on risk of ischemic heart disease.

Established risk factors

It is, however, also possible that workers with shift work more often have an adverse health profile, since shift work is also related to lower socioeconomic status and lifestyle factors. The review by Boggild and Knutsson found that in six out of 13 cross sectional studies, shift workers were more likely to be smokers, in one study shift workers less likely to be smokers, while in six studies no difference in smoking habits was found. The review found no strong indication that alcohol consumption or exercise differed.

The distributions of cardiovascular risk factors among shift workers and day workers were reported in six of the included studies[18-23], of which two used pre-employment information[22;23]. The prevalence of smoking was the same in one study and between 5 % and 12 % higher among shift workers in five studies. In one study, blood pressure and body mass index was related to shift work, while these factors were equally distributed in the remaining five studies. Socioeconomic status was measured in different ways in five studies, where lower status was consistently related to shift work[18;19;21-23].

Methods

Article selection.

Candidate articles for the reference document were selected first on the basis of title and secondly on abstract reading. All candidate articles were retrieved prior to the final selection. Criteria for inclusion in the review were: original research written in English and published in a peer reviewed journal, explicit information on night or shift work, estimates of risk of ischemic heart disease, and use of a prospective design. Complete information on distributions of potential confounders or complete confounder control was not required.

Literature search

The search aimed to identify relevant peer reviewed epidemiological studies written in English providing information on the risk of ischemic heart disease in relation to night or shift work.

The review is based on an updated literature search in Medline (4 April 2008). The search terms were:

((("Survival Rate"[Mesh]) OR ("Mortality"[Mesh]) OR ("Odds Ratio"[Mesh]) OR ("Incidence"[Mesh]) OR ("Risk"[Mesh])) AND (("Cardiovascular Diseases"[Mesh]) OR ("Coronary Disease"[Mesh]) OR (cardiovascular) OR (coronary near disease)) AND (("Chronobiology Disorders"[Mesh]) OR ("Circadian Rhythm"[Mesh]) OR ("Work Schedule Tolerance"[Mesh]) OR (night near work) OR (shift near work) OR (shift work))).

The database search was supplemented by a bibliographic search in previous reviews in the field.

Three researchers performed abstract reading for retrieving relevant articles to minimize the possibility of selective selection.

Article review.

The following elements were extracted from each of the selected articles and tabulated if present: study design, sample size, follow-up time and completeness of participation, exposure assessment, exposure level, case definition and source of information, confounder control (age, gender, blood pressure, blood cholesterol, smoking, physical activity, body mass index, family history of early onset coronary disease, and social class), and exposure response assessments. The strengths and limitations of each study were emphasized. This review describes each study by year of publication. It presents results within studies grouped by comparable outcome assessment, i.e. mortality studies only using fatal cases, and incidence studies combining fatal and non fatal cases into a single outcome.

Results

The Medline search revealed 916 articles of which 54 abstracts were retrieved for reading. Among these 14 full articles with relevance were selected after abstract reading[18-31]. We included two further articles[32;33] identified from two previous reviews[10;34]. Thus, a total of 16 articles were included. Deaths by ischemic heart disease was analysed in 8 of the included studies[19;22;23;25-27;31;33], of which all but one[25] were restricted to male populations. One study used hospitalized cases only[29], and fatal and non-fatal cases of heart or circulatory disease were combined into one outcome in 6 studies[18;20;21;24;25;28]. Three of these studies included female populations [21;25;30]. Two studies included other cardiovascular disorders than ischemic heart disease in their outcome definitions[30;32].

The main characteristics of the retrieved studies are tabulated in table 1, ordered by publication year. Each study is further described in the following text together with strengths and weaknesses.

Description of the individual studies.

Taylor and Pocock[27] performed a historical cohort study with 13 years of follow up among 8603 full time male manual workers identified via pay rolls and employment records from 10 factories in England or Wales. Inclusion criteria were at least 10 years of continuous employment during 1946 to 1968, born before 1920, and alive in 1956. Information on working hours was obtained from company records. 3860 were day workers and 4188 worked in three shift rotas, alternate day and night, double days, rotating 12-hour shifts, or regular night work. Day workers, who during follow-up transferred to shift work, were considered as shift workers, if they completed 6 months of shift work. No censoring by age was used.

A total of 1578 deaths were recorded, of which eight could not be traced in registers. The authors compared the observed number of deaths by ischemic heart disease (ICD-7: 420) obtained from death certificates among day and shift workers with the number of expected deaths controlling for age and calendar time using mortality rates from England and Wales. Among shift workers, 209 deaths by cardiovascular heart disease were observed while 202.8 were expected. Day workers experienced 200 deaths compared to 211.9 expected. The results were reported as being statistically insignificant.

Strengths of this study included relevant follow-up time, high participation rate, and independent information on shift work. A limitation was inadequate confounder control.

Angersbach et al.[32] performed a historical cohort study with 11 years of follow-up among 640 male (370 shift and 270 day workers) workers in a chemical plant. Most shift workers worked alternating day and night shifts with a daily working time of 12 hours. The outcome was defined as hypertension, stenocardia, myocardial infarction, arrhythmias, etc., identified via health records in an occupational health centre or the firm's health insurance. 62 (16.8 %) shift workers and 40 (14.8 %) day workers fell ill during follow up.

The study had several limitations including small study size and inappropriate case criteria and case ascertainment.

Alfredson et al.[24] performed a case-control study among males born between 1911 and 1935 in the catchment areas of two Swedish hospitals. 334 cases with fatal or non-fatal myocardial infarction (ICD 410.00 and 410.99) were included during 1974 – 1976 together with 882 age matched controls. Participants were categorized as having shift work if they worked in occupations where at least 50 % were expected to alternate between day and night work, based on an interview survey performed during 1977. Individual information on occupational code was obtained in 1970. No information on exposure distributions was provided. Age-standardized relative risk comparing subjects belonging to occupations with shift work vs. subjects in other occupations was 1.25 (95 % CI: 0.97-1.62).

Limitations included small study size, indirect exposure information and limited confounder control. In particular, a lack of control for socioeconomic status was a serious limitation in this population based study.

Knutsson et al.[20] performed a historical cohort study with 15 years of follow-up among 504 blue collar workers in the paper and pulp industry. Information on shift work in the period 1968 to 1983 was collected in 1983 and was based on self report or from other sources if participants had deceased. Shift workers worked 3 shift rotas including day, evening and night work. 78 % performed shift work. Ischemic heart disease was defined if participants at the same follow-up occasion reported angina (pain or discomfort in the upper or midsternal region starting during effort and relieved by rest or nitro-glycerine) or myocardial infarction. Self-reported data were checked against health records in most cases. A total of 43 cases (25 myocardial infarction/18 angina) were identified. It is unclear whether fatal cases were included. Relative risk was analysed in different ways, but the statistical methods used were not adequately reported. A non-significant relative risk of 1.4 was reported. Relative risks according to years in shift work were 1.5 (2-5 years, NS), 2.0 (6-10 years, NS), 2.2 (11-15 years, p=0.04, 2.8 (16-20 years, p=0.03), and 0.4 (21 or more years, NS), and a regression coefficient of 0.0774 with a p-value of 0.001 was reported. Controlling for smoking and family status did not alter risk estimates, and years in shift work remained significant after adjusting for age.

Limitations in this study included retrospective self- reporting of shift work and small study size. Although it is a strength that this study used an internal comparison group, residual confounding by age seems likely.

Tüchsen[29] performed a historical cohort study with 4 years of follow-up among all Danish men aged 20-59 in January 1981. The source population was identified in central registers. Occupational coding was obtained from another central register, which again was based on different administrative registers. The validity of this information is unknown. Data on working hours was obtained in 1976 from an interview survey in a sample of 5166 participants, and from a survey among 1728 bakers in 1979, and allocated to all participants by occupational group. Sub-cohorts were constructed based on this information and relative risks were estimated. Historical information on occupational codes was not included. First time hospitalization due to ischemic heart disease (ICD-8: 410-414) during 1981-1984 was identified in the National Inpatient Register. Standardized hospitalization ratios (SHR) were calculated by dividing observed numbers by expected number among those trades with mainly day work (18 trades, e.g.: architects, lecturers, teachers, shop assistants, skilled and unskilled workers) and multiplied by 100. Work predominately at night and early morning (self employed and skilled bakers): SHR=193 (90 % CI 158.3-236.0). Work in occupational groups in which at least 20 % work late evening (taxi operators, self employed in hotels, cooks and waiters): SHR=215 (90 % CI: 192.4-240.1). Work covering 24 hours services (fishermen, traffic staff, shipping and railway staff, bus and road transport staff, rescue service/police): SHR=168 (90 % CI: 151.8-185.5). Work irregular hours (e.g. drivers and production workers): SHR=172 (90% CI: 166.4-182.1). Certain occupational groups within health care were excluded due to a suspected problem with referral bias[35].

The study was limited by unknown validity of occupational job coding, group based and only prevalent exposure assessment, and inadequate confounder control, in particular of socioeconomic factors and smoking.

Kawachi et al.[25] performed a prospective cohort study with 4 years of follow-up among 79,109 women, all nurses, 42 to 67 years old, who in 1988 had answered a question on shift work. The source population was a cohort of nurses established in 1976 where 121,700 females 30 – 55 years of age completed a baseline questionnaire in the Nurses' Health Study. This cohort has been followed biannually with questionnaires to update information on risk factors and major illnesses. In 1988 110,141 eligible participants were asked about the total number of years during which they had worked rotating night shifts (at least 3 nights per month). The authors categorized responses into: never, 1-2, 3-5, 6-9, 10-14 and 15+ years, and into never vs. ever. 40.6 % had never done shift work. The actual status in rotating night work was not asked for. In 1988 those who were deceased, previously had reported myocardial infarction, angina, or cerebrovascular disease were excluded. Comparison of non- responders and responders revealed that non-responders more often were current smokers, had hypertension, diabetes, or hypercholesteroleamia. Among responders duration of shift work was associated with current smoking, BMI, hypertension, diabetes and to higher levels of physical activity.
Cases of non-fatal myocardial infarction were identified by self-report in 1992 and combined with information from medical records, if possible, or else with an interview. Fatal cases were traced in death registers and the cause of death confirmed by medical or autopsy records or death certificates when possible. 292 cases, of which 44 were fatal, appeared.

The age-adjusted risk of fatal and non-fatal disorder was increased to 1.38 (95 % CI: 1.08-1.76), and to 1.31 (95% CI: 1.02-1.68) in multivariate analyses. The fully adjusted risk estimates tended to increase after 6 years of night work, RR=1.60 (95% CI: 1.05-2.42) and did not increase further with longer duration of exposure. A test for linear trend was reported to show a p-value of 0.04 including all women, and a p-value of 0.2 when restricted to shift workers. The age-adjusted relative risk for fatal myocardial infarct was 1.23 (95 % CI: 0.66-2.31) and fully adjusted 1.19 (95 % CI: 0.63-2.23).

This study is strengthened by the use of a socioeconomic homogeneous cohort, and exclusion of already sick participants . Several relevant confounders were considered, but it was unclear how smoking, which was quite strongly related to night shift work, was controlled for in the analyses. Some important limitations included partial self-reporting of outcome and self-reported retrospective exposure information with incomplete information on nightwork. The analyses of fatal outcome were based on few cases.

McNamee et al.[22] performed a case-control study nested among male manual workers aged 50 years or under and hired between January 1950 and December 1992. Information on shift work was based on company records characterising each work day and was complete for 72 % of participants. A worker was exposed if he did shift work for at least one month, and 2/3 worked in shift. Shift work was predominantly a three part shift, one week, forward rotation system. Total number of years in shift work was calculated. A mean of 23 years of observations was performed of which an

average 10 years was spent at the plant site. No information on shift work was collected for employment periods prior to or after employment at the plant.
All deaths and their causes were notified to the company from United Kingdom Office of Population Censuses and Surveys from 1950 to 1992. A total of 467 died from ischemic heart disease before the age of 76 years.
Information on height, blood pressure and weight was available from pre-employment medical examination. Smoking status was known for only 53 %. Type of work was extracted from job titles. Controls were matched by year of hire and age.
Odds ratios were calculated with conditional logistic regression analysis and included other risk factors. Tests for trend were performed after excluding day workers.
Adjusted odds ratio for shift work vs. day work was 0.85 (90 % CI: 0.65-1.12). There was no increasing trend in risk with increasing duration of shift work.

Strengths of this study included independent retrospective exposure information and thorough confounder control using pre-employment information on cardiovascular risk factors. A limitation was that exposure information was not informed for periods worked outside the company, and missing information on smoking for a large proportion.

Steenland and Fine did a nested case-control study within a cohort of 21,491 male workers at four plants. Cases were all who died of ischemic heart disease while working or within one week of work. Information on follow-up period, calendar time, source of outcome information and completeness of information was not provided in this brief communication. 163 cases who also provided adequate personal records of work type were included and 5 controls were selected matched on age, race, plant,

and work status. Controls with prior indication of heart disease were excluded. No information on smoking, obesity, socioeconomic status, or blood lipids was available. Type of fixed shift (day, afternoon, or night) at date of death or match date was traced in personal records. A previous change of shift from one type to one held at the date of death or match date was also traced. Odds ratios were calculated by conditional logistic regression analyses. The odds ratio for evening shift vs. day shift workers was 1.01 (95 % CI: 0.66-1.52) and for night shift workers vs. day shift workers 0.64 (0.28-1.47).

This study was published as a brief communication. Due to limited information on material and methods, strengths and weaknesses could not be assessed.

Tenkanan et al.[28] performed a prospective cohort study with up to 7 years of follow-up among 1,806 males employed in 5 industrial companies. The study group was a sub- cohort within the Helsinki Heart Study, a placebo-controlled coronary prevention program among males, 40-55 years old at entry. Participants from industry were volunteers recruited and screened twice in 1982, with non high-density lipoprotein cholesterol >= 5.2 mmol/l, no evidence of current ischemic heart disease or any other illness. A sample of participants only screened once was also included. Previous diagnosis of cardiovascular disease was allowed. At the end of the coronary prevention study, around 1987/88, 1806 out of 2794 eligible participants completed a psychosocial questionnaire and were followed up in registers through 1993. Working hours were recorded on a 6-point scale. Working 2 or 3-shifts, irregular and night work were combined into one category as shift work, and also 2-shift and 3-shift work (incl. irregular and night work) was analysed. 71% of the participants were blue collar

workers and 37 % of the total cohort had shift work. Information on smoking, alcohol consumption, physical activity, BMI, blood pressure, and serum lipids was collected in 1982. Psychosocial work loads were informed by the questionnaire in 1986/87, and occupational grouping (white or blue collar) was based on occupational codes. Ischemic heart disease (ICD-9: 410-414, number of cases not reported) was followed up in hospital and death registers. A Previous hospitalization for a heart disease was also informed.

The effects of shift work were assessed in Cox proportional hazard analysis. Adjusted hazard ratios were 1.38 (95 % CI: 1.01-1.89) for all shift workers vs. all day workers and 1.30 (95% CI: 0.91-1.97) for blue collar shift vs. blue collar day workers. Analysis after exclusion of previously diagnosed CVD and those on gemfibozil showed similar risk estimates.

When compared with day time academic and clerical workers 2-shift workers had an increased relative risk of 1.9 (95 % CI: 0.98-3.5) and 3-shift workers 1.6 (95% CI: 0.94-2.7).

Limitations of this study included a relatively low participation rate and lack of analysis of drop outs, allowance of previously diseased persons in the cohort, and low precision of risk estimates. A strength was thorough confounder control.

Bøggild et al.[18] performed a 22 years follow-up study among 5249 male workers, aged 40-59 years, recruited from different industries. The cohort was established in 1970-71 as part of the Copenhagen male study with the purpose of studying cardiovascular risk factors. Information on shift work was obtained by questionnaire and confirmed by interview. 22 % did not work solely during day time and these were

classified as shift workers. No information on duration of shift work was obtained. At follow-up in 1985-86 change in shift work was assessed. Information on life style factors, height and weight, blood pressure, fitness value, and social class was established at baseline. 1006 incident cases of fatal or nonfatal ischemic heart disease (ICD-8:410-414) were traced in national registers on hospitalization and death. Adjusted relative risk of 0.9 (95 % CI: 0.7-1.1) among shift workers was estimated by Cox proportional hazard method. There was no increase in risk among shift workers who changed to day work.

Strengths of this study included a high participation rate, long and complete follow-up, thorough confounder control, and adequate statistical power. Considering the lack of expected associations a major limitation is the crude exposure data that may result in serious misclassification and low chance to identify cardiovascular effects related to shift work.

Knutsson et al.[21] performed a population based case control study including 2006 cases of fatal and non fatal myocardial infarction and 2642 controls matched on gender, geographic region and age. There was no information on participation rates. The study used data from two parallel programs on heart diseases. The source population was all citizens living in one of two regions in Sweden, aged 45-70 years, and no previous diagnosed heart disease at start of follow up in 1992 and 1993 respectively. Cases were traced for 2 to 3 years in death and hospital discharge registers, and at relevant hospital units in the areas. Shift work was assessed by questionnaire for the most recent 5 years of work. It was not stated how information concerning deceased cases was collected. If participants indicated they had shift work

or work hours between 6 p.m. and 6 a.m. they were categorized as shift workers. Participants reporting having working hours between 10 p.m. and 6. a.m. were further categorized as night workers. All others were classified as day workers. Among male cases and controls 18 % and 12 % respectively reported shift work, and among females these figures were 16 % among cases and 10 % among referents.
Information on smoking, job strain, and educational level was obtained by questionnaire as well.
Risk among shift workers was analysed among males and females by logistic regression. Among males the relative risk was 1.3 (95% CI: 0.9 -1.8) adjusted for job strain, educational level and smoking. Among females it was 1.6 (95 % CI: 0.8-3.1).

Limitations here included insufficient reporting of participation rate, exposure assessment covering only a short time period, and different calendar periods. There was limited confounder control, in particular a lack of adjustment for socioeconomic level considering that this is a population based study.

Virtanen et al.[31] used data from the Finish Longitudinal Census Data File containing national censuses since 1970. A closed cohort was established, restricted to 50 % of employed males, aged 25-64 in 1980, and with the same occupation in 1975 and 1980. The cohort was followed from 1980 to 1994. Working hours were categorized into regular day, 2-shift evening, or 3-shift night based on a job exposure matrix, the FINJEM, allocating the exposure by occupational codes. Information on age, marital status, education, and income was included from registers. Occupational class and category were coded into socioeconomic indicators.

Diagnosis of ischemic heart disease was traced in death register and 8378 cases were identified (ICD-9: 410). The relative risks related to work factors including shift work were only given if it was larger than 1.00, irrespective of statistical significance. Thus no result was presented since relative risk was less than unity.

Strengths of the study included independent measures of exposure and outcomes, large study size and adequate adjustment for socioeconomic group. A limitation was the use of aggregated exposure assessment and strong likelihood of considerable exposure misclassification.

Karlsson et al.[33] performed a historical follow up study among 2354 shift and 3088 day workers. The cohort included male workers employed for at least 6 months between January 1940 and the end of 1998, from two pulp and paper plants, and less than 60 years old at first employment. Duration of shift work was assessed using company records with information on job title, employment periods, and work place. Participants were categorized as never having worked shifts (electrical and mechanical maintenance workers, laboratory workers, and cleaners) and those who had shift work (workers in barking, grinding, screening, boiling, bleaching , and paper manufacturing) for less than 5, 5-9, 10-19, 20-29, or 30 years or more. No censoring by age was used. 662 deaths by ischemic heart disease were identified from 1952 to 2001 in the national death register. Relative risks adjusted for age and calendar year were estimated. The overall relative risk was 1.11 (95 % CI: 0.95-1.30). Relative risks according to exposure category were 0.85 (95 % CI: 0.30-2.38), 0.97 (95 %: 0.56-1.67), 0.83 (95 % CI: 0.58-1.19), 1.02 (95 % CI: 0.77-1.36), and 1.24 (1.04-1.49) respectively.

A strength of this study was the use of independent exposure information.

Limitations were inadequate confounder control and small sample size.

Fujino et al.[19] used data from The Japanese Collaborative Cohort Study for the Evaluation for Cancer Risk (JACC Study). The study included 17.649 males with full time employment, 40 to 59 years old between 1988 and 1990, and free of myocardial infarction, and cerebrovascular diseases. Shift work was assessed at baseline by questionnaire asking for the most worked shift during the participants working life. 83.7 % of participants were categorized as day workers (mainly worked day time), 11.4 % as rotating shift workers (mainly worked alternate day and night time), and 4.9 % as night workers (mainly worked night). Questionnaire based information about smoking, alcohol, hypertension, diabetes, educational level, perceived stress, hours of walking, exercise, and job type was also obtained.
86 deaths by ischemic heart disease (ICD-10: I20-I25) were traced in data held by JACC study centres until the end of 2003.
Adjusted relative risks were estimated using Cox proportional hazard method, and for night workers it was 1.23 (95 % CI: 0.49-3.10), while for shift workers it was 2.32 (95 % CI: 1.37-3.95).

The quality of exposure information was low in this study and there were few cases.

Tüchsen et al.[30] used data from the Danish Working Environment Cohort Survey. The study included 2853 male and 2664 female respondents, who in 1991 were between 20 and 59 years old, and gainfully employed. The study sample was drawn as

a random sample from the general population. Participants who at base line interview reported that they worked two or three shifts, fluctuating, permanent evening, night, or early morning, or other non-day work were categorized as exposed to working irregular hours and 17 % were exposed. Interview based information about a number of work related psychosocial, physical and chemical exposures, smoking, and BMI was also obtained.

562 cases of first hospital contact (ICD-8: I390-I458 or ICD-10: I00-I99) were traced in registers from 1991 to 2002.

Adjusted relative risk was estimated by log linear regression and was for irregular work hours 1.31 (95 % CI: 1.06-1.63).

This study was limited by the use of an inadequate outcome definition, qualitative exposure measures, and lack of control of socioeconomic status.

Yedegarfer and McNamee[23] performed a nested case control study in a different industrial cohort than the one reported on previously[22]. The cohort included all men aged 50 years or under, who began working as industrial workers between January 1950 and December 1998 at a company site in the nuclear fuel industry. Information on daily working hours was extracted from company records using the same methods as in a previous study[22]. A definition of shift work was used if workers had been engaged in non-day work for at least 30 days. The pattern of shift work schedules included 3-shift systems and double day (mornings and afternoons) shifts. Total number of years in shift work was also extracted together with shift work status at end of employment.

Records from pre-employment physical examination were used to obtain information on height, weight, blood pressure and smoking. Social class was inferred from job codes.

During 1950-1998 635 deaths by ischemic heart disease (ICD: 410-414) before the age of 75 were traced in death registers. 635 referents were drawn, matched on age, year of hire, and vital status. A mean of 25.5 years of observations was performed while the mean duration of employment at the factory was 10.5 years for cases and 8.3 for referents. No information on shift work before or after hiring at the plant was collected.

Adjusted relative risk was estimated using conditional logistic regression. Additional analyses were performed to evaluate potential health related selection into shift work. Adjusted odds ratio for death from IHD was 1.10 (90 % CI 0.91-1.32) compared with day workers without social class in the model and 1.03 (90 % CI: 0.83-1.28) when this was included. Exposure response analysis revealed increasing odds ratios with increasing duration of shift work compared with day workers, but a test for trend was not significant.

This study had the same strengths and limitations as the study by McNamee el al.[22]

General findings

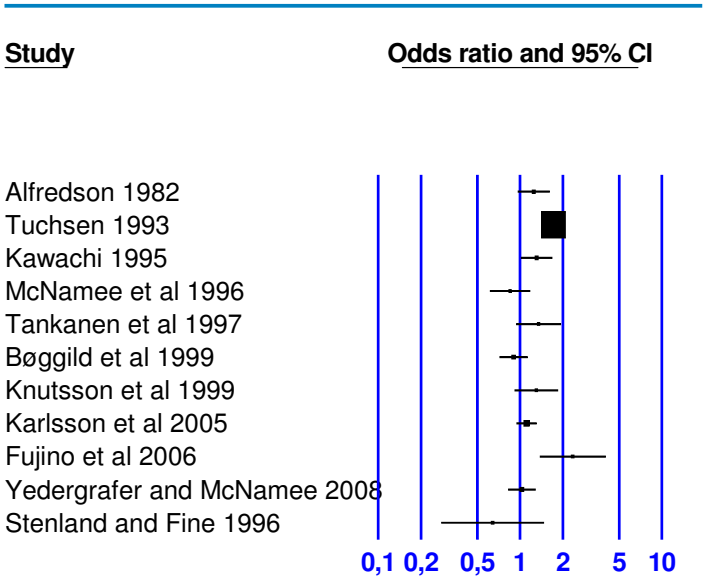
Overall risk

A total of 16 studies on shift work and risk of ischemic heart disease published between 1972 and 2008 were found. Point estimates of relative risks ranged between

0.64 and 1.15 in eight[18;22;23;26;27;31-33] and between 1.25 and 1.35 in six[20;21;24;25;28;30]. The remaining two studies reported relative risk estimates around 2[19;29].

The case definitions varied. Two studies included diseases that are not normally considered as ischemic heart disorders[30;32] in their outcome definition and will not be considered any further. Among the remaining fourteen studies, eleven provided point estimates and 95 % confidence intervals of relative risk as seen in Figure 1.

Figure 1. Point estimates of relative risk of ischemic heart disease among night shift workers obtained from eleven epidemiologic studies. The size of the square symbol reflects the number of participants in the studies.



The fourteen relevant studies used outcome definitions that fell into two main categories. Seven used mortality data (fatal cases) alone[19;22;23;26;27;31;33], six used incidence data by combining morbidity and mortality data [18;20;21;24;28;29]. One study

provided separate risk estimates for fatal cases alone as well as on non fatal cases and on the combinations of these[25].

Mortality studies

Eight studies analysed the risk of death by ischemic heart disease[19;22;23;25-27;31;33]. Table 2 gives an overview over studied populations, numbers of cases, exposure comparisons, point estimates of relative risk and confounders considered. Two studies used employed males from general populations[19;31], five studies included male workers from industrial settings, of which two were among two different groups of employees at the same facility[22;23]. Information on working hours was collected from company records in the five industry based cohorts[22;23;26;27;33] while two studies used self-reporting[19;25] or an aggregated measure[31]. Two studies included cases after the age of 78[27;33]. The number of cases varied from 44 among 110,141 nurses followed for four years[25] to 8,378 cases among 507,000 employed males followed for 13 years[31]. In the remaining studies number of cases ranged from 86 to 662 with follow up periods from 15 to 49 years. Participants were mainly allocated to shift work categories on the basis of not working during daytime hours. Most of these were engaged in rotating shifts including night work. Years of shift work was the only measure used in exposure response analyses[22;23;33]. One study analysed risk in relation to evening and night work[31], and two studies in relation to working mainly/fixed at night[19;26]. Three studies performed limited confounder control[26;27;33] while the remaining studies controlled to some extent for socioeconomic factors, blood pressure, smoking, and body mass index. Two studies with 44[25] and 86[19] cases reported increased risk estimates of 1.19 and 2.35 respectively, while risk estimates ranged from 0.64 to 1.11 in six studies with between 163 and more than 8000 cases.

Two studies found no positive trend with years in shift work[22;23], while one study reported a positive trend and a relative risk of 1.24 among those with at least 30 years of shift work[33].

Incidence studies

Seven studies used incidence data, combining mortality and morbidity data. Table 3 provides an overview of the results of these studies. Two studies provided information on the number of fatal and non-fatal cases[20;25]. Fatal and non-fatal cases of myocardial infarction was the outcome definition in three studies[21;24;25], while four studies used outcome definitions that in principle included angina, other acute or chronic ischemic heart diseases, as well as myocardial infartion[20;28;29;36]. Four studies used occupational cohorts[18;20;25;28] and three studies used general population sampling[21;24;29]. Information on working hours was based on self-report in five studies[18;20;21;25;28], while an aggregated measure allocated on the basis of information on trade was used in two studies[24;29]. The number of cases varied from 43 among 540 workers followed for 43 years to 1006 among 5249 workers followed for 22 years. Participants were considered exposed to shift work if they were engaged in different shift systems, worked at night, had irregular work hours, or they were engaged in trades where the likelihood of working at night was considered high. Night work was not an explicit exposure criterion in all studies, but shift work was considered to include work between 2400 and 0600 in most. Two studies performed exposure-response analyses[20;25], while risk in relation to type of shift pattern was analysed in one study[21]. Three studies performed limited confounder control[20;24;29], while four studies considered potential confounders more adequately. One study reported a risk estimate of 0.9[18], five reported estimates between 1.25 and 1.40, while one study reported risk

estimates of around two[29]. One study reported a positive trend in risk in an analysis where workers with more than 20 years of shift work were excluded[20] and one study reported a relative risk of 1.21 among those with less than six years and 1.51 among those with more than 6 years of rotating night shifts[25], as compared with never having nightwork.

Gender effects

Only two studies provided risk estimates among exposed females. Kawachi[25] et al. reported relative risks of 1.19 for fatal cases, 1.34 for non-fatal cases and 1.31 for the combined case definition, and Knutsson[21] et al. reported and odds ratio of 1.3, which was of the same size as among males.

Discussion

Shift work that includes work at night may be linked to ischemic heart disease. Theories include unfavourable shifts in metabolic factors connected to disrupted circadian rhythm, increases in stress, or unfavourable changes in smoking and eating habits. The evidence on these mechanisms is considered to be limited[10].

This review included 16 studies. Of these, two provide limited contributions due to inadequate outcome definition[29;32]. In the remaining studies estimates varied from 0.64 to 2.25 with most risk estimates around unity. Studies that reported on mortality data generally showed lower risk estimates than studies that reported on incidence data.

Selection

Participation rates and completeness of follow up were high and above 80 % in 11 studies, around 65-70 % in 2 follow-up studies[25;28], and not reported in one nested case control study[21]. In one study non-responders tended to experience more ischemic heart disease than responders (RR: 1.19, 95 % CI: 0.96 – 1.48) and more often were current smokers (29.7 % vs. 18.5 %). We agree with the authors of that study, that major bias due to selection would be unlikely[25], but non-participation related to exposure could not be ruled out. One case control study, that did not report participation rate, used retrospective exposure assessment [21], making it vulnerable to exposure related self-selection of cases into the study. Another issue of selection bias relates to the healthy worker mechanism, especially when comparing disease risk in working populations with the risk in general populations. One study used such external comparisons and risk in relation to shift work might have been underestimated in that study[27], since day workers had slightly reduced risk compared

to the external reference group. Most other studies used cohorts free of disease in their follow-up and, in general, health related selection into shift work would be unlikely in the included studies. The risk in relation to years in shift work could be underestimated, especially in studies of death by ischemic heart disease, if non-fatal ischemic heart disease predicts change to day work. This was not the case in a cohort of Finnish nurses, and the authors concluded that the possibility that those with cardiovascular problems leave their work place was independent of work schedule[37]. However, many give up shift work within a few years, possibly due to adjustment difficulties, leaving the more robust and perhaps healthier workers still employed in shift work. This could lead to attenuation of exposure-response relations when using cumulative exposure measure. The issue of a "healthy shift worker survivor effect" attenuating exposure response relations was addressed in two connected studies, and the suggestions of such an effect could not be precluded, although the effect seemed small[22;23].

Information bias

Misclassification of outcome and/or exposure may be systematically skewed. Recent studies have shown very different associations between certain psychosocial factors and sub-diagnosis of ischemic heart disease. This warrants careful consideration of the possibility of reporting bias. For this reason separate analyses of sub-diagnoses of ischemic heart disease should be performed [38-40]. It is less likely that a diagnostic coding of cause of death would be systematically related to exposure status, but the accuracy of the death certificate diagnosis of ischemic heart disease is modest[41]. Misclassification of outcome in studies based on mortality would thus tend

to underestimate a true effect of shift work. It was characteristic that mortality studies showed lower risk estimates than incidence data studies.

On the other hand outcome measures that are based, or partly based, on self report, or on hospitalization, may inflate risk estimates due to referral bias[35;40;42]. In Denmark, for example, almost half of those hospitalized for ischemic heart disease had a sub-diagnosis of angina[2]. Three incidence studies only included myocardial infarction[21;24;25] . In these studies relative risks were 1.3, 1.25, and 1.3 respectively. In four studies all sub-diagnoses of ischemic heart disease were included and these showed risk estimates of 0.9, 1.4, 1.4 and around 2 [18;20;28;29]. Separate analyses on sub-diagnoses of heart disease were not performed. Kawachi et al.[25] showed lower risk estimates for fatal than for non-fatal myocardial infarction, but the number of cases was low. As mentioned above, risk estimates concerning ischemic heart diseases in relation to psychosocial loads may be substantially biased due to differential reporting of symptoms. Angina possibly contributed a substantial proportion of cases in some studies[18;20;28;29] but risk estimates in these were of comparable sizes to those reported in studies that only accepted myocardial infarction as the outcome. This indicates that self-reporting of symptoms or self-referral to hospital may not be strongly related to exposure status.

Considering the hypothesis of disturbed circadian rhythm, work schedules that include the time period between midnight and early morning are expected to have higher impact than working hours outside this time range. Most of the studies stated that shift work most often included work at night. Some studies also categorized workers with poorly defined work hours, or work in afternoon or evening as shift workers, although not all of these were necessarily exposed to work at night. Such misclassification would likely not be differential and thus inaccurate exposure

assessment could underestimate the risk. Bøggild et al.[18] and Yadegarfar et al.[23] reported equivocal relative risks. They classified irregular and afternoon/evening (non night shift workers) as shift work. No information on the distribution of evening and night shift workers was provided, and thus, the possibility for misclassification cannot be ruled out. Four studies included separate analyses on the type of shift work[19;21;26;31], with and without nightwork, where no clear indications were found for stronger effects among workers mainly working during nights compared to shift work that did not include working at night. Five studies obtained information of working hours from fairly complete company records[22;23;26;27;33], three studies used aggregated measures[24;29;31], and six used self-reporting[18-21;25;28]. We expect that independent exposure information at the individual level, as obtained from company records, would provide higher quality exposure information. In these studies relative risk estimates ranged from 0.64 to 1.11, and thus, the studies with better quality exposure information showed no tendency of increased risk. Except for the Boggild study[18], all studies based on self-reported working hours showed increased risk estimates. Two of these used retrospective exposure assessment[20;21], making them vulnerable to recall bias.

Confounding and effect mediators

Important risk factors for ischemic heart disease include, blood pressure, blood lipids, body mass, smoking, and socioeconomic status. An effect of shift work may be mediated through unfavourable changes in behavioural factors, if these are related to shift work. This mechanism should be considered when controlling potential confounders in studies on shift worker's risk of ischemic heart disease. Controlling pre-employment smoking, blood pressure and blood lipids would be adequate and this

was done in two of the studies[22;23]. Smoking was reported on in 6 studies[18;20;21;23;25;28], and was generally more frequent among shift workers. A modest attenuation in risk estimates was seen after multivariate adjustment, although residual confounding due to imprecise assessment of smoking and possibly also other lifestyle factors still would be possible[43]. Five studies provided information on crude (or only age adjusted) as well as fully adjusted risk estimates. The adjusted risk estimates were all close to unity and only minor changes in risk estimates in the expected direction appeared after adjustment, two showing increases[22;28], and three showing decreases[18;23;25].

Some papers have reported that starting shift work is related to gains in body weight[44-47], more smoking, and unfavourable changes in blood lipids[17;48-51]. These studies provide some evidence for an effect of shift work mediated through these factors, and thus controlling such factors in the analyses would tend to attenuate an effect of shift work. A recent study among newly educated Danish social and health care workers, on the other hand, showed quite a strong relation between smoking and later engagement in shift work[52]. Looking at the five studies that provided adjusted as well as unadjusted risk estimates did not indicate that confounder control had major impact on the crude risk estimates [18;22;23;25;28]. Modest changes were seen, indicating that high quality information on potential confounders and mediators are important to disentangle any true effects of shift work from residual confounding, especially when estimates of relative risk, as in most of the included studies, are around unity or slightly above. As mentioned, a minority of the studies reported adjusted and unadjusted estimates to guide interpretation of the results. However, disentangling effect mediation from true confounding would require studies that included pre-employment and repeated assessments of potential confounding/mediating factors.

Bøggild[18] and Yadegarfar[23] found that socioeconomic factors confounded risk estimates even though both studies used industrial cohorts, where socioeconomic factors are expected to be more comparable than in studies using general population samples. Most other studies that used industrial cohorts, where social background could be considered quite homogeneous, did not perform further controls of socioeconomic factors, leaving possibilities for residual confounding[20;25;28;33].

Exposure response

The impact of cumulative exposure to shift work has not been clearly stated in the theories about shift work and ischemic heart disease, and it is also unclear whether effects of shift work are expected to cease or continue after exposure has ended. However, most studies considered workers exposed if they ever had been engaged in shift work for some minimum of time. Follow-up commonly ended when participants reached a certain age, usually the mid seventies. On the basis of this it seems that most authors anticipate some gradual development of disease, and that the risk will increase according to cumulative exposure.

Five studies[20;22;23;25;33] analysed risk in relation to years with shift work. Two studies found an increase in risk according to years with shift work, one[33] after more than 30 years, and the other[20] after more than 10 years, but with a decrease after more than 20 years. Both these studies had important limitations. Two studies of good quality found no relation to years of shift work[22;23]. One study among females showed an increased risk after 6 years, but the number of cases in that study was small[25].

Other relevant data

Boggild and Knuttsson considered the evidence for an unfavourable relation of shift work to cardiovascular risk factors like cholesterol and blood pressure and found mixed results. Although no firm conclusion could be drawn, some studies indicated that cholesterol and triglycerides seemed to be raised[10]. Based on cross-sectional data, Karlsson et al. suggested that metabolic disturbances (obesity, unfavourable levels of blood lipids) may be related to shiftwork[16;17]. Two recent longitudinal studies found that shift work was related to increased weight gain/obesity[45;47]. One study found an increased risk of starting smoking and a decreased risk for not quitting smoking among shift workers[51]. Thus, some evidence exists that metabolic disturbances and changes in smoking habits are related to starting in shift work and supports the hypothesis that the risk of ischemic heart disease could be mediated through such changes.

Concluding remarks and overall evaluation

Fourteen studies reporting on the risk of ischemic heart disease in relation to night shift work were found. Seven reported mortality data, six incidence data and one reported on both types of data. The range of relative risk estimates derived from these studies was from 0.6 to 2.3. Two mortality data studies, both with few cases, reported an increase in risk. The interpretation of these studies was limited by the low number of cases and unknown validity of exposure information. Six mortality studies reported relative risks around unity. Of these, two used exposure information of high quality and thorough confounder control. However, inaccurate outcome assessment in mortality studies may tend to underestimate a true effect of shift work. Seven studies used incidence data combining non-fatal and fatal cases. All but one study reported relative risk slightly above unity. These associations were statistically significant in two studies. Interpretation of these results is limited by methodological problems such as inadequate confounder control, differential exposure misclassification, and an inability to rule out selection bias.

The available evidence concerning the influence of type and duration of shift work, as well as gender, on the risk of ischemic heart disease is too limited to permit any conclusions on these issues.

Some supportive evidence for an effect of shift work mediated by unfavourable changes in metabolic mechanisms and smoking habits has appeared.

Given the criteria of the Scientific Committee of the Danish Society of Occupational Health, this review finds limited evidence of a causal association between night shift work and ischemic heart disease(+).

Reference List

(1) Selwyn A, Braunwald E. Ischemic heart disease. In: Braunwald E, Isselbacher K, Petersdorf R, Wilson J, Martin J, Fauci A, editors. Harrison's Principles of Internal Medicine. 11 ed. New York: McGraw-Hill Book Company; 1987. 975-982.

(2) Heart Statistics 2004. København: Danish Heart foundation and National Institute of Public Health; 2004.

(3) Galobardes B, Smith GD, Lynch JW. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. Ann Epidemiol 2006; 16(2):91-104.

(4) Gonzalez MA, Rodriguez AF, Calero JR. Relationship between socioeconomic status and ischaemic heart disease in cohort and case-control studies: 1960-1993. Int J Epidemiol 1998; 27(3):350-358.

(5) Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Arch Intern Med 2007; 167(16):1720-1728.

(6) Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Eur Heart J 2007; 28(19):2375-2414.

(7) Hardoon SL, Whincup PH, Lennon LT, Wannamethee SG, Capewell S, Morris RW. How much of the recent decline in the incidence of myocardial infarction in British men can be explained by changes in cardiovascular risk factors? Evidence from a prospective population-based study. Circulation 2008; 117(5):598-604.

(8) Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. Circulation 2004; 109(9):1101-1107.

(9) Unal B, Critchley JA, Capewell S. Modelling the decline in coronary heart disease deaths in England and Wales, 1981-2000: comparing contributions from primary prevention and secondary prevention. BMJ 2005; 331(7517):614.

(10) Boggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. Scand J Work Environ Health 1999; 25(2):85-99.

(11) Knutsson A, Boggild H. Shiftwork and cardiovascular disease: review of disease mechanisms. Rev Environ Health 2000; 15(4):359-372.

(12) Kristensen TS. Cardiovascular diseases and the work environment. A critical review of the epidemiologic literature on nonchemical factors. Scand J Work Environ Health 1989; 15(3):165-179.

(13) Moore-Ede MC, Richardson GS. Medical implications of shift-work. Annu Rev Med 1985; 36:607-617.

(14) European Foundation for the Improvement of living And Working Conditions. Third European survey on working conditions 2000. Luxembourg: Office for Official Publications of the European Communities; 2001.

(15) European Foundation for the Improvement of living And Working Conditions. Fourth European Working Condition Survey. Luxembourg: Office for Official Publications of the European Communities; 2007.

(16) Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. Occup Environ Med 2001; 58(11):747-752.

(17) Karlsson BH, Knutsson AK, Lindahl BO, Alfredsson LS. Metabolic disturbances in male workers with rotating three-shift work. Results of the WOLF study. Int Arch Occup Environ Health 2003; 76(6):424-430.

(18) Boggild H, Suadicani P, Hein HO, Gyntelberg F. Shift work, social class, and ischaemic heart disease in middle aged and elderly men; a 22 year follow up in the Copenhagen Male Study. Occup Environ Med 1999; 56(9):640-645.

(19) Fujino Y, Iso H, Tamakoshi A, Inaba Y, Koizumi A, Kubo T et al. A prospective cohort study of shift work and risk of ischemic heart disease in Japanese male workers. Am J Epidemiol 2006; 164(2):128-135.

(20) Knutsson A, Akerstedt T, Jonsson BG, Orth-Gomer K. Increased risk of ischaemic heart disease in shift workers. Lancet 1986; 2(8498):89-92.

(21) Knutsson A, Hallquist J, Reuterwall C, Theorell T, Akerstedt T. Shiftwork and myocardial infarction: a case-control study. Occup Environ Med 1999; 56(1):46-50.

(22) McNamee R, Binks K, Jones S, Faulkner D, Slovak A, Cherry NM. Shiftwork and mortality from ischaemic heart disease. Occup Environ Med 1996; 53(6):367-373.

(23) Yadegarfar G, McNamee R. Shift work, confounding and death from ischaemic heart disease. Occup Environ Med 2008; 65(3):158-163.

(24) Alfredsson L, Karasek R, Theorell T. Myocardial infarction risk and psychosocial work environment: an analysis of the male Swedish working force. Soc Sci Med 1982; 16(4):463-467.

(25) Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Speizer FE et al. Prospective study of shift work and risk of coronary heart disease in women. Circulation 1995; 92(11):3178-3182.

(26) Steenland K, Fine L. Shift work, shift change, and risk of death from heart disease at work. Am J Ind Med 1996; 29(3):278-281.

(27) Taylor PJ, Pocock SJ. Mortality of shift and day workers 1956-68. Br J Ind Med 1972; 29(2):201-207.

(28) Tenkanen L, Sjoblom T, Kalimo R, Alikoski T, Harma M. Shift work, occupation and coronary heart disease over 6 years of follow-up in the Helsinki Heart Study. Scand J Work Environ Health 1997; 23(4):257-265.

(29) Tuchsen F. Working hours and ischaemic heart disease in Danish men: a 4-year cohort study of hospitalization. Int J Epidemiol 1993; 22(2):215-221.

(30) Tuchsen F, Hannerz H, Burr H. A 12 year prospective study of circulatory disease among Danish shift workers. Occup Environ Med 2006; 63(7):451-455.

(31) Virtanen SV, Notkola V. Socioeconomic inequalities in cardiovascular mortality and the role of work: a register study of Finnish men. Int J Epidemiol 2002; 31(3):614-621.

(32) Angersbach D, Knauth P, Loskant H, Karvonen MJ, Undeutsch K, Rutenfranz J. A retrospective cohort study comparing complaints and diseases in day and shift workers. Int Arch Occup Environ Health 1980; 45(2):127-140.

(33) Karlsson B, Alfredsson L, Knutsson A, Andersson E, Toren K. Total mortality and cause-specific mortality of Swedish shift- and dayworkers in the pulp and paper industry in 1952-2001. Scand J Work Environ Health 2005; 31(1):30-35.

(34) Bonde JP, Andersen JH, Frost P, Kaergaard A, Kolstad HA, Thulstrup AM. [Health examinations in connection with night work]. Ugeskr Laeger 2007; 169(21):2005-2007.

(35) Tuchsen F, Andersen O, Olsen J. Referral bias among health workers in studies using hospitalization as a proxy measure of the underlying incidence rate. J Clin Epidemiol 1996; 49(7):791-794.

(36) Boggild H, Suadicani P, Hein HO, Gyntelberg F. [Shift work, social class and ischemic heart disease in middle-aged and elderly men. A 22-year follow-up in the "Copenhagen Male Study"]. Ugeskr Laeger 2000; 162(13):1882-1886.

(37) Kivimaki M, Virtanen M, Elovainio M, Vaananen A, Keltikangas-Jarvinen L, Vahtera J. Prevalent cardiovascular disease, risk factors and selection out of shift work. Scand J Work Environ Health 2006; 32(3):204-208.

(38) Macleod J, Davey SG, Heslop P, Metcalfe C, Carroll D, Hart C. Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study of Scottish men. BMJ 2002; 324(7348):1247-1251.

(39) Macleod J, Smith GD. Re: "does job strain increase the risk for coronary heart disease or death in men and women? The Framingham offspring study". Am J Epidemiol 2004; 160(10):1031-1032.

(40) Nielsen NR, Kristensen TS, Prescott E, Larsen KS, Schnohr P, Gronbaek M. Perceived stress and risk of ischemic heart disease: causation or bias? Epidemiology 2006; 17(4):391-397.

(41) Coady SA, Sorlie PD, Cooper LS, Folsom AR, Rosamond WD, Conwill DE. Validation of death certificate diagnosis for coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. J Clin Epidemiol 2001; 54(1):40-50.

(42) Macleod J, Davey SG, Heslop P, Metcalfe C, Carroll D, Hart C. Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study of Scottish men. BMJ 2002; 324(7348):1247-1251.

(43) Davey Smith G, Ebrahim S. Mendelian Randomization: Genetic Variants as Instruments for Strengthening Causal Inference in Observational Studies. In: Weinstein M, Vaupel J, Watcher K, editors. National Research Council. Biosocial Surveys. Committee on Advances in Collecting and Ulilizing Biological Indicators and Genetic Information on Social Science Surveys. Washington: Commitee on Population, Division of Behavioral and Social Sciences and Education. The National Academies Press; 2008.

(44) Atkinson G, Fullick S, Grindey C, Maclaren D. Exercise, energy balance and the shift worker. Sports Med 2008; 38(8):671-685.

(45) Biggi N, Consonni D, Galluzzo V, Sogliani M, Costa G. Metabolic syndrome in permanent night workers. Chronobiol Int 2008; 25(2):443-454.

(46) Di LL, De PG, Zocchetti C, L'Abbate N, Basso A, Pannacciulli N et al. Effect of shift work on body mass index: results of a study performed in 319 glucose-tolerant men working in a Southern Italian industry. Int J Obes Relat Metab Disord 2003; 27(11):1353-1358.

(47) Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K et al. A Longitudinal Study on the Effect of Shift Work on Weight Gain in Male Japanese Workers. Obesity (Silver Spring) 2008.

(48) Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. Occup Environ Med 2001; 58(11):747-752.

(49) van Amelsvoort LG, Schouten EG, Kok FJ. Duration of shiftwork related to body mass index and waist to hip ratio. Int J Obes Relat Metab Disord 1999; 23(9):973-978.

(50) van Amelsvoort LG, Schouten EG, Kok FJ. Impact of one year of shift work on cardiovascular disease risk factors. J Occup Environ Med 2004; 46(7):699-706.

(51) van Amelsvoort LG, Jansen NW, Kant I. Smoking among shift workers: More than a confounding factor. Chronobiol Int 2006; 23(6):1105-1113.

(52) Nabe-Nielsen K, Garde A, Tuchsen F, Hogh A, Diderichsen F. Cardiovascular risk factors and primary selection into shift work. Scand J Work Environ Health 2008; 34(3):206-212.

Table 1. Main characteristics of 16 epidemiological studies of shift work and risk of ischemic heart disease, 1972-2008

Study, year and location	Coronary disease	Design, study population, study period and no. of participants (participation rate), no cases	Source of exposure information	Exposure criteria, prevalence in study base.	Source of outcome information	Covariates controlled for	Exposure response assessment
Taylor and Pocock, 1972, UK[27]	Fatal cases (ICD-7: 420)	Historical cohort of full time male manual workers, hired between 1946 and 1968, born before 1920 and alive in 1956, 1956-1968, 8767 (99.75), 444.	Employment records.	10 years of shift work (3-shift weekly or rapid rotating, alternate days and nights, double days, others): 48 %.	Death certificates	Age, calendar year.	No
Angersbach, 1980, Germany[32]	hypertension, stenoncardia, myocardial infarction, arrhytmias, etc.	Historical cohort of workers in a chemical plant, 1966-1977, 640 (100), 62.	n.r.*	Working in 2 shift systems: n.r.	Records from occupational health centres.	None.	No.
Alfredson, 1982, Sweden[24]	Fatal and non fatal cases (ICD 410.00 and 410.99)	Case-control study among males born 1911-1935 in the catchments areas of Södertälje and Huddinge hospitals, 1974-1976, 334 cases (85) and 882 age matched controls (91).	Census data collected in 1970 or 1975.	Occupations where at least 50% in a census reported continuously day and night work: n.r.	Cause of death register and medical information system.	Age.	No.
Knutsson et al, 1986, Sweden[20]	Fatal and non fatal cases (angina pectoris or myocardial infarction)	Historical cohort of male blue-colour workers at a paper and pulp manufacturing plant, 504 (95.5), 1968-1983, 43.	Self-reported or from relatives, friends, or supervisors (if deceased) at end of follow up.	3-shift rota. 78.2 %.	Death certificates, hospital and occupational health unit records assessed according to WHO criteria by cardiologist	Age, hypertension, smoking, and marital status.	Duration (years) of shift work: 0, 2-5, 6-10, 11-15, 16-20, 21+.
Tüchsen, 1993, Denmark[29]	Hospitalized cases (ICD-8: 410-414).	Sub cohorts of employed males working mainly day or abnormal working hours, aged 20-59 years on 1 January 1981, 1981-1984, 406,969 (100), 5960.	International standard classification of occupation (ISCO) code obtained from administrative registers combined into occupational groups with known working hours based on information obtained in pervious surveys.	Occupational groups in which at least 20 % have abnormal working hours: 40 %	National InPatient Register.	Age.	No.

*n.r.=not reported

Table 1. (continued)

Kawachi, 1995, USA[25]	Non fatal and fatal cases (myocardial infarction).	Prospective cohort study among 79,109 female nurses, 1988-1992, (71,8), 292. Participation rate in 1992: n.r.	Self reported by questionnaire.	Had worked or worked at least 3 nights per month in addition to days and evenings: 59 %.	Self reported in 1992 and review of medical records by physicians (definite and probable cases). Death certificates or medical records (fatal cases).	Age, smoking, blood lipid, hypertension, diabetes,BMI, level of physical activity, use of hormones, alchohol, parental history of MI, aspirin use, vitamin E intake.	Duration (years) of shift work: 0, 1-2, 3-5, 6-9, 10-14, 15 or more.
Steenland and Fine, 1996, USA[26]	Fatal cases (ICD-9: 410-414)	Nested case-control study among 21,491 male workers at four plants, Follow up time not reported., 163 cases, n.r., and 5 plant, age, and race matched controls, n.r.	Company records	Second shift (evening workers): 22-23 %. Third shift (night workers): 5-6 %	Source not reported	Age, race, plant	No.
McNamee et al, 1996, UK[22]	Fatal cases (ICD-8: 410-414).	Nested case-control study among male industrial workers under 50 years of age, who started work between January 1950 and 31 December 1992 at a nuclear fuel element factory, 1950-1992, 467 cases <76 years (100) and one individual age-matched control was drawn (100).	Primarily obtained from pay codes and supplemented by information from register of dosimeters and medical notes in occupational health records.	Worked (mainly) in a 3 shift systemd for a period of one month or more: 59%.	Death certificates	Age, pre employment: systolic and diastolic blood pressure, BMI, height, and smoking.	Duration (years) of shift work: day workers, 0.1-1.9, 2.0-4.9, 5.0-9.9, >=10.0.
Tankanen et al, 1997, Finland[28]	Fatal and non fatal cases (ICD-9: 410-414)	Prospective cohort study among 1806 male blue-collar workers, 1987/88-1993 (64.6). Participants were included among volunteers in the Helsinki Heart Study.	Self reported by questionnaire.	Worked 2 or 3-shift, irregular work and night work: 37 %.	Death and hospital discharge register.	Age, smoking, cholesterol, blood pressure, BMI, physical activety, and alcohol consumption.	No.
Bøggild et al, 1999, Denmark[18]	Fatal and non fatal cases (ICD-8: 410-414)	Prospective cohort study of 5249 male workers in different industry, between 40-59 years old, (The Copenhagen male study), 1971-1993 (87), 1006.	Self reported by questionnaire and interview.	Worked irregular hours, shift work, often night work: 22 %.	National Health Service Register.	Age, tobacco, weight, height, social class, fitness value, sleep.	No.

Table 1 (continued).

Knutsson et al, 1999, Sweden[21]	Fatal and non fatal cases (myocardial infarction)	Population based case-referent study among all citizens in Stockholm and Vasternorrland counties, 40-70 years old, 1992-1994 (Stockholm), 1993-1995, 2006 cases, n.r. and 2642 gender region, and age matched controls, n.r.	Self reported by questionnaire.	During the most recent 5 years of work worked beyond day time (6 am to 6 pm): 10-12 % or between 10 pm and 6 am: 2-3 %.	Hospital departments, hospital discharge and death certificates in combination with necropsy findings. Medical records evaluated by cardiologists.	Age, gender, smoking, job strain, educational level..	No.
Virtanen et al, 2001, Finland[31]	Fatal cases (ICD-9: 410).	Prospective cohort of 507,000 males between 25 and 64 years old in 1980, 1981-1994, n.r., 8,378	Job exposure matrix (FINJEM) developed at the Finnish Institute of Occupational Health	Worked evening or three-shift night: n.r.	National death register.	Age, marital status, follow up period, professional status, income, education and other occupational factors	No.
Kalsson et al, 2005, Sweden[33]	Fatal cases (ICD-9: 410-414)	Historical cohort of 5442 male workers in pulp and paper manufacturing, 1952-2001(95), 662.	Company files.	Job titles engaged in shift work: 42 %.	National Cause of Death Register.	Age, calendar periods.	Duration (years) of shift work: Never, <5, 5-9, 10-19, 20-29, >=30.
Fujino et al, 2006, Japan[19]	Fatal cases (ICD-10: I20-I25).	Prospective cohort of 17,649 employed men, 1988-2003 (87), 86.	Self reported by questionnaire.	In their working life mainly worked night: 4.9 % or mainly alternate night and day time: 11.4 %.	Cause of death retrieved annually from the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk.	Smoking, alcohol intake, hypertension/diabetes, educational level, stress, hours of walking, type of job.	No.
Tüchsen el al, 2006, Denmark[30]	Hospitalized cases (ICD-8: I390-I458 and ICD-10: I00-I99).	Prospective cohort of 5517 (2853 males and 2208 females), 1991-2002 (95), 562.	Self reported by interview at baseline.	Not working on permanent day duty: 17 %.	National Patient Register	Smoking, BMI, passive smoking, psychosocial and ergonomic work loads, noise, monotonous work.	No.
Yedegarfer and McNamee, 2008, UK[23]	Fatal cases (ICD:410-414)	Nested case-control study among male industrial worker at a nuclear fuel company, aged less than 50, and hired between January 1950 to the end of 1998. 1950-1998. 635 cases < 76 years (100) and one matched control (age, year of hire), (100).	Primarily obtained from pay codes and supplemented by information from register of dosimeters and medical notes in occupational health records. Work status was imputed for 3.5 % .	Engaged in non day work for at least 30 days: 53 %.	Death register	Height, weight, pre employment blood pressure, smoking, social class.	Tests for trend according to categories of years of shift work: 0, 1-4.9, 5-9.9, and >=10. Duration was also analyzed as a continuous variable.

Table 2. Night shift work and risk of ischemic heart disease, mortality studies. Findings from 8 epidemiologic studies in male or female populations published between 1972 to 2008.

Study, year, country	Follow up period, number, and setting.	Outcome criteria	Exposure comparisons	Measure of risk	Point estimate, (confidence interval or p-value)	Confounders considered
Male populations						
Taylor and Pocock, 1972, UK[27]	1956 – 1968, 8603 manual workers in industry,	ICD-7: 420, n=444	Shift work vs. general population	Standardized mortality ratio	1.03 (p>0.05)	Age and calendar period
Steenland and Fine, 1996, USA[26]	Not reported, 21,491 workers in four heavy equipment plants	ICD-7: 410-414, n=163	Night workers vs. day workers	Odds ratio	0.64 (95 % CI: 0.28-1.47)	Age, race, plant
McNamee et al, 1996, UK[22]	1950-1992, number not reported, industrial workers in a nuclear fuel production facility.	ICD-8:410-414, n=467	Shift work vs. day work.	Odds ratio	0.85 (90 % CI: 0.65-1.12)	Age, pre employment blood pressure, height, weight, smoking, and job status.
Virtanen et al, 2001, Finland[31]	1981-1994, 507,000 employed males in general population	ICD-9: 410, n=8,378	Two shift evening vs. regular day Three shift night vs. regular day	Rate ratio	The authors found relative risk less then unity. Estimates not reported.	Age , marital status, socio economic indicators, calendar period.
Karlsson et al, 2005, Sweden[33]	1952-2001, 5442 workers in pulp and paper manufacturing	ICD-6: 4200-4203, 4209 ICD-7: 4200-4202 ICD-8 and 9: 411-414 ICD-10: I20-I24, n= 662	Shift work vs. day wok	Standardized mortality ratio	1.11 (95 % CI: 0.95-1.30)	Age, calendar time
Fujino et al, 2006, Japan[19]	1988-2003, 17649 employed males.	ICD-10: I20-I25), n=86	Mainly rotting shifts vs. mainly day work Mainly night work vs. mainly day work	Rate ratio	2.35 (95 % CI:1.37-3.95) 1.23 (95 % CI:0.49-3.10)	Age, smoking, alcohol, hypertension, diabetes, stress, physical activity, and job type.
Yedegarfer and McNamee, 2008, UK[23]	1950-1998, number not reported, industrial workers in a nuclear fuel production facility.	ICD-?: 410-414, 635	Non day work vs. day work	Odds ratio	1.03 (90 % CI:0.83-1.28)	Age, pre employment blood pressure, height, weight, smoking, and social status.
Female populations						
Kawachi et al[25], 1995, USA	1988-92, 79,1909 female nurses	Myocardial infarction, n=44	Rotating night work with at least 3 nights per month vs. less night work or day work	Rate ratio	1.19 (0.63-2.23)	Age, smoking, hypertension, diabetes, cholesterol, BMI, contraceptives/hormones, alcohol, parental history, physical activity

Table 3. Night shift work and risk of ischemic heart disease, incidence studies. Findings from 7 epidemiologic studies in male or female populations using combined outcome measure published between 1980 and 2006.

Study, year, country	Follow up period, number, and setting.	Out come criteria	Exposure comparisons	Measure of risk	Point estimate, (confidence interval or p-value)	Confounders considered
Male populations						
Alfredson, 1982, Sweden[24]	1974-1976, n.r., male general populaton.	Fatal or non fatal ICD-410, n=334	Continuously changing day and night vs. not	Odds ratio	1.25 (95 % CI: 0.97-1.62)	Age
Knutsson et al, 1986, Sweden[20]	1968-1983, 504 workers at paper and pulp plant.	Angina pectoris, myocardial infarction, or death by MI, n=43.	Shift work vs. day work	Rate ratio	1.4 ("not significant")	Age and otherwise unclear
Tüchsen, 1993, Denmark[29]	1981-1984, 1,293,888 Danish males aged 20-59 years.	Hospital discharge diagnosis ICD-8: 410-414, 5,966.	Night/early morning work vs. day Later evenings vs. day Rosters covering 24-hours services vs. day Other irregular vs. day	Standardized hospitalization ratio	193 (90 % CI: 58-236) 215 (90 % CI: 192-240) 168 (90% CI: 152-186) 172 (90 % CI: 166-182)	Age
Tankanen et al, 1997, Finland[28]	1987-1993, 1806, employees in industry including white and blue collar workers.	Fatal or non fatal ICD-9: 410-414, n=n.r.	Blue collar shift work vs. blue collar day work	Rate ratio	1.35 (95 % CI: 0.94-1.93)	Age, smoking, lipid, blood pressure, bmi, physical activity, and alcohol.
Bøggild et al, 1999, Denmark[18]	1971-1993, 5249, employees in different industry.	Fatal or non fatal ICD-8:410-414, n=1,006	Non day work vs. day work	Rate ratio	0.9 (0.7-1.1)	Age, smoking, weight, height, social class, fitness value, sleep
Knutsson el al, 1999 Sweden[21]	1993-1995, n. r., inhabitants in specified parts of Sweden	Fatal or non fatal infarction, n=1,417	Shift work vs. day work	Odds ratio	1.3 (1.1-1.6)	Smoking, job strain, educational level
Female populations						
Kawachi et al[25], 1995, USA	1988-92, 79,1909 female nurses	Fatal or non fatal infarction, n=292	Rotating night work with at least 3 nights per month vs. less night work	Rate ratio	1.31 (1.02-1.68)	Age, smoking, hyper-tension, diabetes, choleste-rol, BMI, contraceptives, /hormones, alcohol, history, physical activity
Knutsson el al, 1999 Sweden[21]	1993-1995, n. r., inhabitants in specified parts of Sweden	Fatal or non fatal, n=589 infarction, n=589	Shift work vs. day work	Odds ratio	1.3 (0.9-1.8)	Smoking, job strain, educational level

Appendix 1: Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome. Criteria of the Scientific Committee of the Danish Society of Occupational and Environmental Medicine

The following categories are used.

+++	strong evidence of a causal association
++	moderate evidence of a causal association
+	limited evidence of a causal association
0	insufficient evidence of a causal association
-	evidence suggesting lack of a causal association

Description of categories:

Strong evidence of a causal association (+++):

A causal relationship is *very likely*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with *reasonable* confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association (++):

A causal relationship is *likely*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association(+):

A causal relationship is *possible*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association (0):

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-):

Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

Comments:

The classification does not include a category for which a causal relation is considered as established beyond any doubt.
The key criterion is the epidemiological evidence.
The likelihood that chance, bias and confounding may explain observed associations are criteria that encompass criteria such as consistency, number of 'high quality' studies, types of design etc.

Biological plausibility and contributory information may add to the evidence of a causal association.

Appendix 2: Reviewers' comments and authors' responses

Reviews of first draft

Reviewer 1

Major comments:

1. In general I find that the review is well written. Some minor printing errors exist, though, especially in the tables.

We agree. Manuscript and tables have been revised to diminish printing errors.

2. The review discusses 15 epidemiological studies on shift work and cardiovascular disease. I found one paper that should have been identified when the literature search is followed[1]; this might suggest that it would be relevant to include also a short section on studies that was not included. Another study is not included[2], probably because it is not peer-reviewed. This could also be discussed. I suspect that the conclusion would not change, however, by including these studies, and in general I find the review balanced.

We agree. The study by Steenland and Fine was identified by the literature search and considered relevant for the review. It has been added to the manuscript. Papers that were not peer-reviewed were not included.

3. I find however, that the review is not going into greater details relating to a couple of methodological problems that I think is relevant:

The title and conclusion includes the word "causal", and I'm not comfortable with the use of this. As I have argued in my PhD thesis[3] other aspects in the literature than epidemiological studies on work schedule and heart disease outcomes should be considered before the question of causality can be settled, especially I think that it should be discussed that biochemical risk factors like cholesterol and triglycerides changes with different types of shift work. If the review is to answer the question whether a *causal* relationship between night work and ischemic heart disease exists, other aspects should be included, as well.

We agree. We have included some recent evidence on metabolic disturbances and change in smoking habits related to starting in shift work. A section has been added under the heading "other relevant data". However, we find that an comprehensive review of the literature on change in risk factors, is beyond the objective of this review.

4. Another problem is to choose how to handle information on for instance behavioural changes. Now information is mainly given in the introduction (p. 4, bottom) and is seen as confounders (discussed in the text and tables), but if for instance smoking is considered a pathway in the causal chain, then it should not be regarded as and handled as a confounder

[1] Steenland K, Fine L. Shift work, shift change, and risk of death from heart disease at work. Am J Ind Med, 1996; 29:278-81

[2] Åkerstedt T, Alfredsson L, Theorell T. Arbetstid och sjukdom – en studie med aggregerede data. Stockholm: Statens Institut för Psykosocial Miljömedicin, 1987

[3] Bøggild H. Shift work and heart disease. Faculty of Health Sciences, University of Aarhus, 2000: http://www.dadlnet.dk/dmb/dmb_phd/doc/henrik_boggild_phdafh.pdf

using regression models. If however, behaviour is seen as a confounder, then I think also other factors related to the model introduced should be discussed and preferably included.

We agree. We have extended the discussion section especially on the confounder vs. effect mediators.

5. Also, I think the recent findings related to metabolic syndrome being more prevalent among shift workers (see for instance work by Karlsson et al) should be mentioned, as this suggests a possible explanation for the association between shift work and ischemic heart disease.

We agree. Please refer to our responses above to comment 4 and 5.

6. I think more focus should be given to discussion of methods, as only some of the methodological questions are addressed. Selection mechanisms (especially primary selection) are only sparsely dealt with, as also the discussion on exposure assessment (type of work, number of night shifts, the ergonomic outline of the work schedule etc) could be discussed in more details.

We partly agree. The discussion section has been extended on methodological issues including primary selection into shift work which seems to relate to smoking. Likewise, some extension in the discussion of comparability, strengths and limitations in exposure measurement methods have been made.

7. Especially, I note that the Knutsson study (p. 11) is considered flawed by using internal comparisons. As I have argued in my PhD-thesis, the choice of reference group is crucial for examining shift work, and although day workers are not necessarily the best group, internal comparisons with the day-working groups are probably better than using external reference groups, as large differences in other factors related to ischemic heart disease might exist between shift and day working groups.

We partly agree. We find that appropriate control of age may be less well in this study especially in the exposure response analyses. We have made this clearer in the manuscript.

8. I finally suggest a little more rigor in describing the individual studies, especially when extracting strengths and weaknesses.

We partly agree. Some revisions have been made in these descriptions.

Minor comments:

9. Page 3, third paragraph: I think the discussion of outcome should be transferred to page 27 ff. It is not necessary for understanding the introduction of the study design.

We agree, the transferral has been made.

10. Page 4, second paragraph, last sentence: What do you mean by "…worked *between* at night..."?

This was one more printing error, which have been corrected.

11. Page 23, first paragraph: While I agree that coding is probably not related to social class, social class is related to survival of ischemic heart disease, and could theoretical bias the effect.

We think that this type of bias would tend to inflate risk estimates based on mortality data. However these studies in general showed no increase in risk estimates.

12. Page 27, last paragraph: We recalculated among others the SMR from the Taylor and Pocock paper in the 1999 review, RR (unadj) 1.00 (0.84-1.18)

We are aware of these recalculations, which are close to the one we achieved by diving the observed number with the number expected(= 1.03).

13. Page 28, first paragraph: I do not agree that "tertiary", health-related selection out of shift work is unimportant. It is dependent on the type of work and policy of employers, in several early studies there were large selections.

The evidence we have found on this issue did not indicate that shift workers with heart disease are substantially more prone to leave work than day workers with heart disease.

Reviewer 2

The review has been commissioned by the Danish Board of Industrial Injuries and the objective is to review the epidemiologic evidence for a causal association between shift work and risk of ischemic heart disease.

The review is very systematically done and generally of high quality. I have one key comment and some suggestions regarding the organization and presentation of the material.

1. My key comment refers to the final conclusion: "…that the evidence for a causal relation between work at night and ischemic heart disease is insufficient (0)." It is not stated in the review but I assume that the (0) refers to a standardized classification scheme used in Danish work environment research and that the wording also follows that classification. The (0) makes one believe that the conclusion is the strongest negative option in that classification scheme. The wording taken literally appears to mean that the evidence falls short of leading to the conclusion that causality is present but without further qualifications. As such it encompasses all possibilities except that causality is proven. I had expected, and hoped for, a more nuanced conclusion, but perhaps that would not be in accord with the classification scheme that is being used. This needs clarification. Of the seven studies in table 3 all but one have raised relative risks, albeit modestly so. I cannot see that lack of statistical power is a reason to discard their results. It is certainly correct that each of the studies has limited precision due to small numbers, but collectively the numbers are not small. Residual confounding may certainly affect some of the results but not all and indeed several of the studies seem to have quite reasonable confounding control. It is essential that the review is clear about the interpretation of these results and that a clear justification is given for that interpretation.

We agree. We have included the committee's criteria as an appendix into the manuscript. The overall evaluation has been changed to "limited evidence" (+), which we find reflects the evidence level more appropriately.

2. I also have some more editorial comments. The Introduction has some methodological discussions about the disease and about the exposure. I would suggest that these are moved to the methods section after the presentation of how studies were selected. I also suggest adding a discussion about the consequences of using only fatal cases rather than all cases, since this is done in a large proportion of the studies. I am a little bit uneasy about the broad diagnostic category of ischemic heart disease that is being analysed, but I assume this was a given when the project was launched.

We agree. We have moved descriptions of the methods used from the back ground section into the general findings section.
We have made a distinction between studies using mortality data where risk estimates to some extend could be interpreted as reflecting prognostic effects as well as causal effects and accuracy of diagnosis probably is quite modest. All of these studies except one reported relative risks around or below unity.
We have now excluded two studies from the general result and discussion section, and table 3 since these used too broad outcome criteria (Tüchsen,2006; and Angersbach). Three studies used fatal and non fatal myocardial infarction as outcome and four studies the whole range of ischemic heart diseases (i.e. ICD9:410-414) without separate reporting on sub diagnosis. Most of these studies reported a small increase in relative risk.

We discus possible explanations of the heterogeneity/ inconsistency in these results but we were not able to find one single and definite explanation.

3. I find the discussion about the individual studies and about the validity issues almost too systematic. I wonder if the discussion actually would be more useful to the readers if instead the problems of particular relevance for an individual study were discussed specifically in relation to that study and with a view to the study's findings and which impact the problems could have had on the findings. In particular the discussions about the positive and the negative studies would have somewhat different angles. The confounding discussion for example would be different for a positive and a negative study. I also think that the healthy worker effect issue could be brought up in connection with the studies that use SMR or similar methods.

We agree. We have revised the discussion section and discus results in single studies in relation to quality aspects related to selection, comparability, and assessment of exposure and outcome. Some extensions of the discussion section have also been made to comply to this comment.

4. A few smaller points are the following. I am not sure that I agree with the wordings about low statistical power. The effect of the small study size as I see it is that the study has low precision and therefore is going to have smaller weight in the overall assessment, but that would be all. I also wonder about referring to fatal and non-fatal cases as different outcomes. I usually consider the fatal cases as a selected group of all cases. The text needs some language editing.

We agree to comment on the wordings " low statistical power" and have replaced these with the wordings " low precision" or "small study size" where appropriate.
As for the fatal and non fatal cases, please refer to comment 2 above.

Reviewer 3

Thanks for this report, which I found comprehensive and understandable. I attach with a few minor typos highlighted. I didn't know of other studies than those you have reviewed and I think it is definitely the case that a formal meta-analysis cannot be carried out. A few issues:

1. I have highlighted in yellow places where the wording reads oddly or there appear to be typos.

Thank You, we have revised the manuscript accordingly.

2. Page 4 - 5: perhaps worth explaining in more detail that behavioural factors such as smoking, drinking, diet could either be influenced by shift work (and therefore mediators of an effect of shift work on health) or could be confounders, with the same underlying factor (low socio-economic position for example) being related both to adverse behavioural profiles and to being more likely to be engaged in shift work.

We have extended the background and discussion sections on this issue. Please also refer to the answer to comment 3 of reviewer 1.

3. On page 14 in your italicised summary of the nurses health study paper you say that as this was a socio-economically homogeneous cohort and there was good confounder control for the effects observed. You seem to imply that it should be taken more seriously. However it is worth pointing out that the nurses health study has found many things that appear due to confounding, such as use of vitamin E supplements being protective against coronary heart disease (found observationally but not found in randomised controlled trials), effects of beta-carotene on health outcomes, etc etc. Thus confounding seems to be just as much as an issue in the nurses health study as in other studies. I attach a book chapter which briefly reviews this in it's first few pages (the reference is Davey Smith G, Ebrahim, S. Mendelian randomization: Genetic variants as instruments for strengthening causal inference in observational studies. In: National Research Council (2008). Biosocial Surveys. Committee on Advances in Collecting and Utilizing Biological Indicators and Genetic Information on Social Science Surveys. Weinstein M, Vaupel JW, Wachter KW, eds. Committee on Population, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press).

We agree. We have included this reference in our discussion section.

4. There have been many studies now suggesting that disruption of sleep patterns lead to higher body mass index/obesity; perhaps this issue deserves separate discussion.

We agree. We have included a part on this issues in the discussion section. Please also refer, again, to the answer to comment 3 of reviewer 1.

5. Regarding the section on confounding (confounding page 29) it would be good if the tables reported the effect estimates before and after adjustment for confounding factors. It is more important to be able to see how adjustment for confounding factors influences the estimate than concentrate on whether the finally adjusted estimate is "significantly" different from the null. If there is a reasonable degree of attenuation of the effect estimate on adjustment for confounders then it is likely that measurement error in the confounders will lead to under-adjustment and residual confounding. This can be best ascertained by examining the degree to which adjustment and cumulative adjustment influences the effect estimates.

We agree, but only few studies reported both crude as well as partly and fully adjusted risk estimates. These studies and the crude and adjusted estimates are now included in the discussion section.

Reviews of second draft

Reviewer 1
I think the new version is much more balanced and the conclusive (+) is in agreement with my own opinion. I found that all of our comments have been satisfactory dealt with.
You might take advantage of the delay to include the newest figures for cardiovascular mortality in the introduction; the National Board of Health just yesterday published figures for 2002-6

Reviewer 2
I have looked at your responses to all the comments that you received on the first draft and I think that they are highly receptive and
appropriate as are the revisions of the draft. Is there anything more that you expect from us reviewers at this point or can we close the
books?

Reviewer 3
Thanks for the report and the response to reviewers; this now looks fine to me.