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Shift work and cardiovascular events: systematic review and meta-analysis

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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by

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A thesis submitted in partial fulfillment
of the requirements for the degree of
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Abstract

The prevalence of shift work is increasing in the general population. There is conflicting epidemiologic evidence on the association between shift work and cardiovascular disease. We performed a systematic review and meta-analysis of observational studies that measured shift work-cardiovascular disease associations. We screened 12,350 articles and identified 35 eligible studies. The pooled risk ratios (RR) for myocardial infarction, all coronary events and ischemic stroke were 1.23 (95% confidence interval [CI] 1.15 to 1.31, $I^2 = 0$), 1.24 (95% CI 1.10 to 1.39, $I^2 = 85\%$) and 1.05 (95% CI 1.01 to 1.09, $I^2 = 0$), respectively. The population-attributable risks from shift work for myocardial infarction, all coronary events and ischemic stroke in Canada would be 7%, 7.3% and 1.6%, respectively. We found no evidence of publication bias. We report significant yet relatively modest associations for shift work and cardiovascular events. These results have implications for public policy and occupational medicine.

Keywords

cardiovascular disease, cerebrovascular disease, coronary heart disease, heart, ischemic heart disease, meta-analysis, myocardial infarction, morbidity, mortality, night work, shift work, rotating work, stroke, systematic review, work schedule

Dedication

गुरु गोविन्द दोनों खड़े काके लागु पाए|

बलिहारी गुरु आपनी गोविन्द दियो बताये|| - संत कबीर

Guru Gōvinda dōnōṁ khaṛē kākē lāgū pā'ē,
balihārī Guru aapanī, Gōvinda diyō batāyē – Santa kabīra

❖❖❖❖❖

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Chapter 1 Introduction and literature review

1 Overview of objectives

The objective of this thesis is to evaluate whether and to what extent shift work is associated with an increased risk for cardiovascular disease. We conducted a systematic review and meta-analysis of observational studies that met our eligibility criteria. We defined shift work as any work schedule other than day shifts, and cardiovascular disease included both morbidity and mortality. We also assessed whether overall mortality in shift workers was higher. We appraised the quality of evidence by considering the validity, applicability, heterogeneity and precision of included studies, following recommendations by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[1]

2 Scope of the problem

Ischemic heart disease and cerebrovascular disease are the leading causes of death world-wide. In 2008, more than 23% of all deaths were attributed to these two conditions.[2] Moreover, they accounted for 48% of all deaths from non-communicable diseases. The incidence of these conditions is gradually decreasing in high income countries, but rising swiftly in developing countries.[3] According to World Health Organization statistics, heart disease, stroke and diabetes mellitus are estimated to reduce gross domestic product between 1 and 5% in low- and middle-income countries experiencing rapid economic growth.[2] In Canada, heart disease and cerebrovascular disease were responsible for 27% of all deaths in 2008, making them the second most common cause of death in Canada after cancer.[4]

One strategy for reducing the burden of non-communicable diseases is risk factor identification and management. For cardiovascular disease, age, sex and family history are non-modifiable risk factors. Conversely, hypertension, diabetes mellitus, dyslipidemia, smoking, obesity and physical inactivity are modifiable risk factors.[5] The management of the latter has improved substantially over the past four decades, decreasing cardiovascular morbidity and mortality in developed countries.[6] Yet the economic costs of cardiovascular disease and cerebrovascular disease remain staggering.[7] Estimated costs of heart disease and stroke, which include physician services, hospital

costs, lost wages and decreased productivity, was $20.9 billion in Canada in 2005 alone. These are estimated to reach $28.3 billion in 2020.[7] Total costs are higher in the United States with *annual* expenses expected to increase to $470.3 billion in 2020 from $272.5 billion in 2010.[8] Given these figures, there is considerable need to implement measures that further reduce disease incidence.

Concomitantly, the rate of decline of cardiovascular disease incidence in developed countries has slowed.[9] A rapidly aging population, particularly but not exclusively in developed nations, poses increasing burdens to already harried health-care systems.[9] Attempts to decrease the incidence of cardiovascular disease, which encompasses heart disease and cerebrovascular disease, have led researchers to search for hitherto unrecognized cardiovascular risk factors. One such risk factor of growing concern is work environment.[10] On average, full-time working individuals spend roughly 8 hours at work, which constitutes about one third of their day.[11] Various exposures at work, work-stress in particular, have been identified as predictors of cardiovascular disease.[12] Shift work, a specific type of work schedule, is increasingly recognized as a cardiovascular risk factor.

3 Definition of shift work

In 1990, the International Labour Organization defined working in shifts as "a method of organization of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers."[13] The inception of shift work dates back to the advent of the Industrial Revolution. The shift system was introduced to allow manufacturing companies to work around the clock. This transformation in working hours began with the typical three-shift schedule: morning, evening and night shift. Over time, new shift work schedules have been introduced to meet the demands of a growing, post-industrialized economy. The classification of various shifts as reported in the General Social Survey (2005), conducted by Statistics Canada is as follows:

a. evening shift – starts late in the afternoon or evening and ends before midnight.
b. night shift – starts close to midnight with work overnight and ends early in the

morning.

c. rotating shift – workers keep rotating between morning, evening and night shifts. The rotation can be either clockwise or counter-clockwise. A clockwise (forward) rotation changes from morning to afternoon to night, while the counter-clockwise (backward) rotation changes from afternoon to morning to night. The time period on a particular shift may vary depending on the workplace.
d. split shifts – the shift is divided into two or more distinct periods (for example, 8 to 10 a.m. and 4 to 6 p.m. for pre- and post-school programs).
e. on call or casual – there is no prearranged schedule and workers are called to work when a need arises (e.g. supply teachers or "home call" for physicians).
f. irregular shifts – the shifts change, but they are prearranged a week or two in advance (e.g. commercial airline pilots).
g. other shifts – all other shifts that are not "day" work, but cannot be grouped in any of the above categories.

Shift work is generally defined as working in any shift other than the regular day shift beginning around 9 a.m. (± 2 hours) and ending around 5 p.m. (± 2 hours). We will consider this "exclusionary" principle to be our definition of shift work, unless otherwise specified.

4 Prevalence of shift work

Due to economic growth and globalization, many industries have adopted different shift work strategies to cater to the needs of consumers. According to the third European Union Survey on Working Conditions (2000), conducted among 15 European countries, only 27% of the sample population were so called 'standard daytime workers' who were not (a) working more than 40 h/week, (b) working more than 10 h/day, (c) working in shifts, (d) working at night, (e) working on Sunday, (f) working part-time, or (g) working on Saturday.[14] In the United States, the Bureau of Labour Statistics (2004) reported that 14.8% of full-time salaried workers were shift workers, amounting to some 14,767,144 individuals.[15] The proportion of shift work was higher in males than in females (16.7% vs. 12.4%). The prevalence of shift work was greatest among workers in service

occupations, such as protective services (50.6%) – which include police, firefighters and security guards – and food preparation and serving (40.4%); and among those employed in production, transportation, and material moving occupations (26.2%).

In Canada, the proportion of shift workers increased from 22% in 1992 to 28% in 1998 and slipped back to 25% in 2005.[16] These estimates were obtained from a target population employed full time (i.e. > 30 hours/week) and excluded students. People holding part time jobs are more likely to work shifts, as are students.[16] These exclusions suggest that survey data underestimate the true prevalence of shift work in Canadian workers.

The manufacturing industry is no longer the only industry in which shift work is required. According to the General Social Survey (2005), conducted by Statistics Canada, the proportion of shift workers was highest in the "Accommodation and food services industries", with 52.7% of workers in these industries working in shifts.[16] "Transportation" and "warehousing" were other large sectors, with 39.5% and 37.7% employed as shift workers, respectively. Whereas the service industry had a high percentage of shift workers, manufacturing industries still had the highest total number of shift workers (Table 1).

According to the Survey of Labour and Income Dynamics (2005), more men work in the manufacturing industry than women. By contrast, the health care and social assistance sectors have the highest total number of female shift workers.[17] For workers employed in law enforcement, hospital medicine and emergency services, working in shifts is crucial. Economic development coupled with rapid globalization has created conditions in which service and retail industries work around the clock as well. Many jobs that were once day jobs now require some form of shift work. The prevalence of shift work is therefore likely to increase.[18]

Unfortunately, the rise in shift work is a consequence of the demands of society. These demands will increase in the future particularly in low- and middle-income countries with rapidly developing economies. Thus, the population exposed to shift work is growing. According to the 2000-2001 Canadian Community Health Survey, over 50% of shift

workers in Canada reported having "no choice" but to work in shifts to remain employed.[19] It follows that shift work is an unavoidable consequence of the current economy.

5 Shift work and "the economic benefit"

Shift work has a macroeconomic advantage as it helps to reduce unemployment in a region by increasing the availability of employment opportunities. As previously mentioned, for many individuals, the choice is between shift work and no work at all, and so shift work allows such individuals to be gainfully employed.[19]

Table 1. Full-time workers aged 19 to 64 by industry and shift work status in Canada

Industry	Total workers '000	Regular day work %	Shift work %
Agriculture, forestry, fishing and hunting	230	65	35
Mining, oil and extraction	302	68	33
Utilities	121	90	10
Construction	888	84	16
Manufacturing	1,717	73	27
Trade	1,716	74	26
Transportation and warehousing	650	61	40
Finance and insurance	904	82	18
Professional, scientific and technical	1,079	87	13
Business, building and other support	448	64	36
Educational services	817	90	11
Health care and social-assistance	1,272	68	32
Information, culture and recreation	607	62	38
Accommodation and food	620	47	53
Other services	544	76	24
Public administration	831	81	19

Adapted from Statistics Canada, General Social Survey, 2005[16]

From a corporation's perspective, an important reason for shift work is increased

profitability. Some companies in the services sector benefit from being able to provide services around the clock rather than for just a few hours per day (consider, for example, international mail courier companies traversing numerous time zones, day or night). In a competitive marketplace, this makes them desirable choices for consumers, in turn increasing profits by employing an effective shift system.

In a manufacturing company, machines used for the production of goods have a stipulated life span whereby, over time, current machines will be replaced by newer machines due to improvements in technology. Given this condition, a rational enterprise will seek to maximize profit on its capital investment in machinery by using these machines to their maximum "life span". The shift system allows these companies to do so and simultaneously increases the productivity of a factory by utilizing space and resources at "off times" (such as overnight) instead of running two separate factories. Therefore, corporate entities are able to decrease the production costs of their products while increasing returns on their capital investments, thereby increasing profits.

The economic advantage of shift work also extends to workers because they receive premiums or extra pay for working in shifts. However, a survey conducted by the United States Bureau of Labour Statistics in 2004 suggested that only 6.8% shift workers worked in shifts for better pay while 54.6% worked in shifts because it was "the nature of their job".[15] Hence, the choice to work in shifts among workers is not necessarily based on economic gains, unlike that of the companies that hire these workers. Unfortunately, shift workers constitute a population at risk for a number of health problems.[19] We now discuss the impact of shift work on general health.

6 Shift work and short-term effects

The ability to adapt to shift work varies for different individuals. Many shift workers develop adverse effects in the short-term.[20]

6.1 Sleep disturbance

A major concern for shift workers is poor sleep quality and quantity, due to circadian rhythm disruption and sociological factors. Shift workers, particularly those working in

evening and rotating shifts, are more likely to cut back on sleep to find time to spend with their family.[16] The time of work and the type of rotation are also important factors affecting sleep habits and sleep hygiene in shift workers. Permanent night shift workers may sleep less than day workers because the level of noise and number of distractions during the day are more common than those at night. Permanent evening shift workers, on the contrary, do not seem to have this problem.[21] Those who work in rotating shifts, irrespective of night or evening hours, find it difficult to adjust to changing schedules, thereby resulting in sleep deprivation.[22] Sleep quality is also affected due to disruptions in sleep pattern and reduced sleep length.[23] As a result of poor sleep, shift workers report higher levels of sleepiness during work, especially night shifts.[24] Sleepiness in shift workers is hazardous as it increases the risk of accidents.[25] The well-publicized workplace catastrophes occurring at Bhopal, Chernobyl and Three Mile Island are evidence of industrial accidents due to human error occurring during night shifts. For professionals like nurses or physicians, working under varying shifts, night work in particular may have negative consequences on the quality of patient care as well as the prognosis of their patients' conditions.[26]

6.2 Psychosocial problems

Effective work-life balance can be difficult to achieve at the best of times; however, having a regular work schedule or some control over shift scheduling makes it easier to achieve this balance.[27] Indeed, those working on-call or in irregular shifts have significantly higher dissatisfaction with their work-life balance in comparison to day workers.[16] The reasons for dissatisfaction are multiple. Spousal working time is one factor that affects work-life balance. Shift workers whose partners are employed part-time are likely to have less satisfaction with their work-life balance than shift workers whose partners are not in the labour force or are day workers.[16] Overall satisfaction levels are considerably lower when both individuals are employed in shift work.[16]

Work-life imbalance often affects psychosocial health. A prospective study following 4,947 male workers of 45 different organizations in Netherlands from 1998 to 2008, reported an adjusted hazard ratio of 1.22 (95% confidence interval 1.02 to 1.46) for

developing depressed mood in shift workers when compared with day workers.[28] Similar results were obtained in a cross-sectional study of US workers.[29] In addition, a longitudinal study over a period of 10 years (1995 to 2005), based on the British Household Panel Survey, reported that men who worked night shifts for more than 4 years were 6 times more likely to report anxiety or depression than day workers (odds ratio 6.08, 95% confidence interval 2.06 to 17.92).[30] The cause for psychological problems in shift workers was attributed to psychosocial work-related factors, lack of social support and limited social interactions because of their working hours.

7 Shift work and long-term effects

Ample literature suggests that shift work is associated with long-term health consequences.[31]

7.1 Gastrointestinal health

The perils of shift work are not restricted to psychosocial health but also include various digestive system disorders. Several cross-sectional studies compared self-reported gastrointestinal symptoms in shift workers and day workers and found a significant increase in such complaints in shift workers.[32-34] A study of 399 American nurses reported a higher risk of irritable bowel syndrome in nurses on rotating shift work compared to nurses working in day shifts (adjusted odds ratio 2.14, 95% confidence interval 1.14 to 3.03).[35] The risk of peptic ulcer disease in permanent night workers was increased when compared to day workers (age-adjusted relative risk 2.00, 95% confidence interval 1.49 to 2.67) in a cohort study that followed 12,127 workers for 18 months.[36] The reasons for digestive system dysfunction in shift workers are not entirely known, but possible mechanisms include abnormal eating habits because of irregular working hours[37], decreased gut defence increasing the risk of Helicobacter pylori infection[38], and disruption of the biological clock[39].

7.2 Cancer

The effect of shift work on breast cancer, especially in nurses, has been studied extensively. A meta-analysis to ascertain the effect of night work on breast cancer, based

on six observational studies, found a significantly increased risk of breast cancer in women working at night compared to those working during the day (summary relative risk 1.51, 95% confidence interval 1.36 to 1.68).[40]

The prospective Japan Collaborative Cohort study found that prostate cancer was increased significantly in rotating shift workers after adjusting for potential confounders (relative risk 3.0, 95% confidence interval 1.2 to 7.7).[41] However, for night workers, the increase in risk was not statistically significant (relative risk 2.3, 95% confidence interval 0.6 to 9.2).[41] A Canadian case-control study showed that prostate cancer increased in full-time rotating shift workers compared to day workers (odds ratio 1.19, 95% confidence interval 1.00 to 1.42).[42] However, a recent retrospective cohort study did not find a significant increase in prostate cancer (odds ratio 1.79, 95% confidence interval 0.57 to 5.68) when comparing rotating shift workers to day workers.[43] Therefore, the evidence on the risk of prostate cancer in shift workers is inconclusive.

Shift work has also been associated with colon cancer, ovarian cancer, endometrial cancer and skin cancer.[44-47] In 2007, after a comprehensive review of literature, the International Agency for Research on Cancer classified 'shift work that involves circadian disruption' as a probable human carcinogen, group 2A.[48] This report suggested that the risk of cancer increases as the number of years of shift work increases. Work at night involving light exposure may cause suppression of melatonin production.[49] Melatonin acts against cancer through multiple pathways involved in cancer cell proliferation and survival.[50]

7.3 Reproductive health

Women employed in shift work, night work in particular, have a higher risk of pregnancy loss than their counterparts working in day shifts.[51] Shift work is also believed to increase the risk of preterm births.[52, 53] Shift work may affect fetal growth, increasing the risk of having infants with low birth weight and small-for-gestational-age babies.[52, 54, 53] A recent meta-analysis pooling risk estimates from observational studies concluded that women working in shifts have a higher risk of preterm delivery (relative risk 1.16, 95% confidence interval 1.00 to 1.33) and low birth weight infants (relative risk 1.27, 95%

confidence interval 1.03 to 1.22) when compared to day-working women.[55] The cause of these adverse outcomes is not completely understood but circadian rhythm disruption leading to hormonal imbalance may be an important contributing factor.[56]

A multi-centre study undertaken in seven European countries studied the effect of shift work on subfecundity, defined as time of unprotected intercourse of ≥ 9 months to get pregnant. The odds ratio of subfecundity in women working in rotating shifts compared to day workers was 1.3 (95% confidence interval 0.9 to 1.3) for the population-based sample vs. 2.0 (95% confidence interval 1.4 to 2.8) for the pregnancy-based sample, where women were recruited during their prenatal visit to the hospital.[57] For men, the risk of subfecundity was the same in rotating shift and day workers.[57] Hormonal disturbance directly due to circadian disruption or indirectly due to psychological stress is the suggested mechanism for impaired fecundity in shift workers.[58] However, subsequent studies have not found an association between shift work and reduced fecundity.[58, 59]

7.4 Cardiovascular risk factors

The American Heart Association has identified the following as major independent risk factors for coronary heart disease: advancing age, male sex, cigarette smoking of any amount, elevated blood pressure, elevated serum total cholesterol and low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol and diabetes mellitus.[5] This section will discuss the known associations between shift work and these risk factors.

Obesity

Obesity is a worldwide epidemic affecting more than 300 million adults.[60] Obesity increases the risk of having abnormal lipid metabolism, diabetes mellitus, metabolic syndrome, hypertension, cardiovascular disease and mortality.[61] Di Lorenzo and colleagues studied the effect of shift work on the risk of obesity using a cross-sectional survey involving anthropometric measurements of 319 glucose-tolerant workers in a chemical industry in Italy.[62] They found that shift workers were significantly more likely

to be obese than day workers (20% vs. 9.7%, $P < 0.05$).[62] The association was significant after adjusting for age and fasting insulin level. Several other studies have also found a higher prevalence of obesity among shift-working individuals.[63, 64] A study of 377 Dutch workers found that for every year of shift work, body mass index increased by 0.12 kg/m^2 ($P = 0.036$), adjusted for multiple confounders.[65] In a longitudinal study of 7,254 Japanese workers, with a 14-year follow-up period, the odds of developing obesity in shift workers was significantly increased. The odds ratios for 5%, 7.5% and 10% increases in body mass index for workers in alternating shifts vs. day workers were 1.14 (95% confidence interval 1.06 to 1.23), 1.13 (95% confidence interval 1.03 to 1.24) and 1.13 (95% confidence interval 1.00 to 1.28), respectively.[66]

Multiple reasons are proposed for the increased risk of obesity in shift workers. Lack of physical activity appears to be important.[67] However, it is not a sole contributor as a large number of shift workers are blue-collar workers employed in manufacturing jobs that involve considerable physical activity, which requires a certain amount of physical fitness. Working at night is associated with poor dietary habits that involve eating unhealthy food and irregular meal frequency, both of which are associated with the risk of obesity.[68] The circadian disruption caused by shift work is also associated with disturbed intestinal rhythm that may lead to a higher likelihood of developing obesity.[69]

Diabetes mellitus

Of the two types of diabetes mellitus, type 2 diabetes is of particular concern as it occurs at a later age when the likelihood of having other cardiovascular risk factors increases.[5] Most cross-sectional studies have reported no difference in the prevalence of diabetes between shift workers and day workers.[62, 70, 71] However, Suwazono et al. followed 5,629 Japanese steel industry workers for 10 years and reported an odds ratio of 1.35 (95% confidence interval 1.05 to 1.75) for developing type 2 diabetes, ascertained as glycosylated hemoglobin (HbA1c) level $\geq$ 6.0%, for rotating shift workers in comparison to day workers.[72] In contrast, a longitudinal study of Japanese blue-collar workers found a statistically non-significant increase in the risk of type 2 diabetes in shift workers when compared to day workers.[73] Recently, Pan and colleagues studied the effects of shift

work on the incidence of type 2 diabetes, ascertained by self-reported questionnaire, using data from two prospective cohort studies, the Nurses' Health Studies I (1988 to 2008) and II (1989 to 2007), including data from 177,184 nurses in the analysis.[74] They reported a pooled across-study adjusted hazard ratio for developing type 2 diabetes for every five years of rotating shift work of 1.05 (95% confidence interval 1.04 to 1.06), suggesting a dose-response relation for shift work and type 2 diabetes.

Dyslipidemia

Serum levels of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides are markers of lipid metabolism in the body, and abnormal lipid metabolism is an important risk factor for coronary heart disease. Nakamura et al. (1997) studied Japanese blue-collar workers cross-sectionally by conducting health check-ups for workers to determine their risk for coronary heart disease. The authors reported higher levels of serum total cholesterol, but not triglycerides, among rotating shift workers in comparison to day workers.[75] In a cross-sectional study conducted in Sweden, Karlsson and colleagues found that working in a three-shift schedule was associated with low HDL cholesterol (odds ratio 2.03, 95% confidence interval 1.18 to 3.28) and high triglycerides (odds ratio 1.40, 95% confidence interval 1.08 to 1.83), after adjusting for potential confounders.[71] A retrospective cohort study involving 5,510 Japanese steel workers reported an adjusted odds ratio of 1.10 (95% confidence interval 1.00 to 1. 21) for hypercholesterolemia among shift workers involved in three-shift rotating work, in comparison to the day workers.[76] Analysis of the same cohort found that the threshold number of years of shift work that caused a 5% increase in total cholesterol was 21 years.[77]

Hypertension

A recent study demonstrated that deleting the sleep-regulating Cry 1 and Cry 2 circadian clock genes in mice causes hyperaldosteronism, in turn causing salt-sensitive hypertension.[78] A prospective cohort study led by Morikawa et al. followed manual male workers of a zipper-and-sash factory in Japan for five years. The incidence of hypertension (defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure

≥ 90 mmHg at annual health examination, or initiation of anti-hypertensive medications) increased in rotating shift workers when compared to day workers for employees aged 18 to 29 (relative risk 3.6, 95% confidence interval 1.4 to 9.1).[79] A prospective cohort study with a 10-year follow-up demonstrated that the incidence of hypertension in male Japanese steel factory workers, aged 15 to 65 years, increased in rotating shift workers in comparison to day workers (odds ratio 1.10, 95% confidence interval 1.01 to 1.20).[80] Similarly, a 14-year retrospective cohort study of Japanese workers found that both systolic and diastolic blood pressure increased in shift workers compared to day workers.[81]

Apart from the increased risk of incident hypertension, shift work also increases the severity of hypertension in patients with mild hypertension.[82] Shift work changes the diurnal variation of blood pressure from a dipper to non-dipper status in patients with hypertension (the normal nocturnal fall in BP does not occur or, if it does occur, is very small).[83] The non-dipper status carries a higher risk of morbidity as it is associated with end-organ damage, and increases the incidence of cardiovascular events and mortality.[84, 85] Of note, hypertension has the highest attributable risk for incidence of stroke and ischemic heart disease mortality of all cardiovascular risk factors.[86, 87]

Metabolic syndrome

A joint consensus statement unifying various clinical definitions for metabolic syndrome defined the metabolic syndrome as the presence of at least three of the following five traits: abdominal obesity; elevated triglycerides and/or small dense LDL cholesterol; reduced HDL cholesterol; hypertension; and elevated fasting glucose levels.[88]

A nested case-control study of 6,712 men and women found that shift workers had higher odds of developing metabolic syndrome than day workers (odds ratio 1.87, 95% confidence interval 1.13 to 3.08).[89] Analysis of data from 738 nurses, both male and female, followed for four years showed that the hazard ratio of developing metabolic syndrome was 5.01 (95% confidence interval 2.15 to 12.11) in night workers compared with day workers.[90] Furthermore, a prospective cohort study of 1,529 Belgian employees with a median follow-up of 6.6 years found that the odds ratio of developing metabolic

syndrome in shift workers vs. day workers was 1.46 (95% confidence interval 1.04 to 2.07) after adjusting for various confounders. A systematic review of the literature that included nine studies, three longitudinal and six cross-sectional, concluded that shift work can lead to metabolic syndrome.[31] However, the magnitude of the association was not reported.

Summarizing the literature, an association between shift work and various cardiovascular risk factors does exist. There is considerable variation in the magnitude of the effect and the association varies by the type of shift work studied. The following section will examine the role of possible confounding factors that should be considered when evaluating the association between shift work and cardiovascular events.

8 Potential confounders

Koepsell and Weiss state, "Confounding occurs in epidemiological research when the measured association between an exposure and disease occurrence is distorted by an imbalance between exposed and non-exposed persons with regards to one or more other risk factors for the disease."[91]

8.1 Age

It is important to adjust for age when studying cardiovascular disease, because of its relative potency as a predictor of cardiovascular events.[92] With aging, the walls of blood vessels lose elasticity resulting in reduced arterial compliance and increased risk for cardiovascular disease. The distribution of age varies across populations and hence adjusting for age or standardizing by age permits a comparison across different populations. In many, but not all economic sectors, shift workers are relatively younger than day workers.[19]

8.2 Sex

The biological pathways governing cardiovascular disease between males and females may differ. More males work as shift workers than females with the exception of certain occupations such as nurses.[16] Hence, it is important to model the effect of sex when

studying the risk of cardiovascular disease in shift workers.

8.3 Socioeconomic status

Socioeconomic status acts as a proxy or composite measure for various underlying factors. Education, income, occupation, geographic locale, living conditions and income inequality are some individual-level risk factors covered under this term. Education and economic status of parents; education and economic status of spouse or life partner; and availability of resources and opportunities for work are external factors that affect the socioeconomic status of an individual. Different ways exist to measure socioeconomic status and these vary from study to study. Each measure has its own limitations and captures a different aspect of socioeconomic status. These measures are certainly co-related but not necessarily interchangeable when considering their effects on health.[93, 94]

Post-secondary education is a prerequisite for most professional workers. Those who do not obtain post-secondary education are likely to be employed as blue-collar workers in comparison to those who do. Blue-collar jobs in factories are likely to have shift system arrangements. Therefore, limited educational attainment increases an individual's likelihood of taking up shift work, yet it is independently related to health numeracy and literacy that are independent risk factors for cardiovascular disease and mortality.[95] Conversely, in the health care industry, higher education is required for a job as a registered nurse or a physician; both professions often involve some degree of shift work. Therefore, the correlation of education with shift work for nurses and other health care providers may be reversed contrary to that for blue-collar workers.

The literature review by Kaplan and Keil concluded that a strong relation exists between socioeconomic status and all-cause mortality.[96] The authors reported that a consistent inverse relationship between various socioeconomic status indicators and cardiovascular disease also exists.[96] A review on observational studies using a life course approach reported that low socioeconomic status in early life and subsequent low socioeconomic status are consistently associated with a higher burden of cardiovascular risk factors and cardiovascular morbidity.[97] Socioeconomic status is also an established risk factor for cerebrovascular disease, especially stroke.[98, 99] Individuals with low socioeconomic

status are less aware of healthy eating habits and in many instances, they cannot afford healthy eating.[100] They may not have full access to insured health care services or may not use these services as often as others may; thus, their first contact with the health care system may occur at a later stage in disease development, by which time preventive measures are no longer applicable.

Thus, socioeconomic status is related to both shift work and cardiovascular disease and so should be considered as a confounder when evaluating the association of shift work with cardiovascular disease.

8.4 Smoking

Smoking of any amount is recognized as an important risk factor for cardiovascular disease.[5] A systematic review of literature conducted by Boggild and Knutsson found a higher prevalence of smoking in shift workers in six of thirteen cross-sectional studies, while the remaining studies did not find statistically significant increases in smoking prevalence.[101] Given the known association of smoking and cardiovascular disease, if smoking is associated with shift work, its effect should be adjusted for when studying shift work and cardiovascular disease.[91] In a prospective study, van Amelsvoort and colleagues followed a group of non-smoking Dutch workers for two years (N = 5743).[102] Over the course of 2 years, 213 workers (3.7% of total sample) took up smoking. The odds ratio of taking up smoking in shift workers vs. day workers was 1.46 (95% confidence interval 1.05 to 2.03), after adjusting for age, education level, sex, job demands and decision latitude, suggesting that smoking can be a consequence of shift work and not merely associated with shift work. While taking up cigarette smoking was one outcome of interest in this study, the authors also studied whether work schedule affected rates of quitting smoking. They found that shift workers were somewhat less likely to quit smoking when compared to day workers, although this result was not statistically significant (odds ratio 0.91, 95% confidence interval 0.67 to 1.23).

In another study quantifying the amount of cigarette smoking, shift-working smokers were found to smoke more cigarettes per day than day-working smokers.[103] Nabe-Nielsen et al. conducted a prospective study to understand the association of smoking and

shift work.[104] Smoking status of 2,826 social and health care helpers or assistants was assessed at baseline, a few weeks before completion of their education. Their shift work status was ascertained through a follow-up questionnaire one year later. Individuals who were identified as smokers at baseline were likely to work in fixed-night or fixed-evening shifts, adjusting for various personal and familial factors that can act as confounders (odds ratio 1.56 [95% confidence interval 1.21 to 2.02] and odds ratio 1.64 [95% confidence interval 1.04 to 2.56], respectively).[104]

The association of shift work and smoking is complex. Smoking may act both as a confounder and as a mediator. Adjusting for socioeconomic class, which is somewhat related to smoking status, does not fully adjust for the effect of smoking. Intrinsic differences between shift and day workers in lifestyle habits might explain the higher prevalence and incidence of smoking among shift workers.

8.5 Alcohol

Drinking alcohol in moderation may have a protective association with the risk of cardiovascular disease.[105] Most studies that have studied differences in alcohol consumption between shift and day workers are cross-sectional. These studies did not consistently find a statistically significant difference in alcohol consumption between exposed and unexposed groups.[106, 107] For example, Romelsjo et al. found that male shift workers in Stockholm were more likely to be heavy drinkers (35 g 100% ethanol per day or more) in comparison to day workers (odds ratio 2.22, 95% confidence interval 1.11 to 4.45) after adjusting for age, education level and living alone/cohabitation status.[75] This association was reversed for female shift workers, although it was statistically non-significant (odds ratio 0.61, 95% confidence interval 0.08 to 4.61).

Unlike smoking, alcohol consumption does not have a linear relationship with cardiovascular risk. The association of shift work and alcohol consumption is not well established. Thus, others have concluded that alcohol consumption does not play a major role in the association of shift work with cardiovascular disease.[101]

8.6 Job type

We defined blue-collar workers as those who perform primarily physical work and whose career paths are relatively restricted and white-collar workers as professional and semi-professional employees.[108] Blue-collar work carries risk that in concert with shift work may lead to an increase in the risk of cardiovascular disease. This claim, although studied extensively, has not yet been definitively established. The Multi-Ethnic Study of Atherosclerosis (MESA) involving 6,814 participants, showed an increased risk of premature atherosclerosis, ascertained as an increase in the mean common carotid artery intima-media thickness, in blue-collar workers after adjusting for age, sex and race/ethnicity (mean difference = 0.22 mm, $P < 0.001$). However, the association became statistically non-significant when cardiovascular risk factors, income and education were co-adjusted.[109] Chen et al. conducted a hospital-based, case-control study in Taiwan, matching 119 cases of first non-fatal myocardial infarction to 238 controls with no known history of myocardial infarction. They reported an odds ratio of 5.3 (95% confidence interval 1.5 to 18.5) for developing myocardial infarction in blue-collar workers vs. white-collar workers.[110] On the contrary, no significant difference in mortality due to coronary disease or stroke was found between white-collar and blue-collar workers in the Honolulu Heart Program.[111]

In conclusion, age, sex, socioeconomic status and smoking status should be considered as confounding variables for the association of shift work with cardiovascular disease.

9 Shift work and cardiovascular disease

9.1 Surrogate markers of cardiovascular disease

The major pathologic changes that lead to cardiovascular disease are atherosclerosis and thrombosis. A crossover study of 36 female nurses found that coronary blood flow decreases when nurses work night shifts in comparison to when they work day shifts.[112] This suggests that shift work leads to hemodynamic imbalance in the coronary circulation. In a study by Puttonen et al., young Finnish males employed in shift work had a higher odds of having carotid plaque (odds ratio 2.08, 95% confidence interval 1.04

to 4.18), when compared to those working in day shifts, after adjusting for multiple confounders.[113] Similarly, mean intima-media thickness was higher in shift workers than day workers (mean difference 0.03 mm, $P = 0.022$). Intima-media thickness is a well-established predictor of vascular events and atherosclerosis, suggesting that male shift workers have a higher burden of cardiovascular morbidity.[114] In a study involving 184 Taiwanese bus drivers, brachial-ankle pulse wave velocity was higher among bus drivers who did shift work in comparison to those who did not, suggesting increased arterial stiffness in shift workers.[115] In another study, a trend for a lower % flow mediated dilatation (P value = 0.08), assessed using ultrasound, was observed among shift compared to non-shift workers.[116] The literature also suggests that other biomarkers of vascular disease, such as C-reactive protein, leukocyte count, homocysteine and peripheral arterial tone, are increased among shift workers.[117-119]

Therefore, existing evidence suggests that surrogate markers of atherosclerosis are increased as a result of shift work.

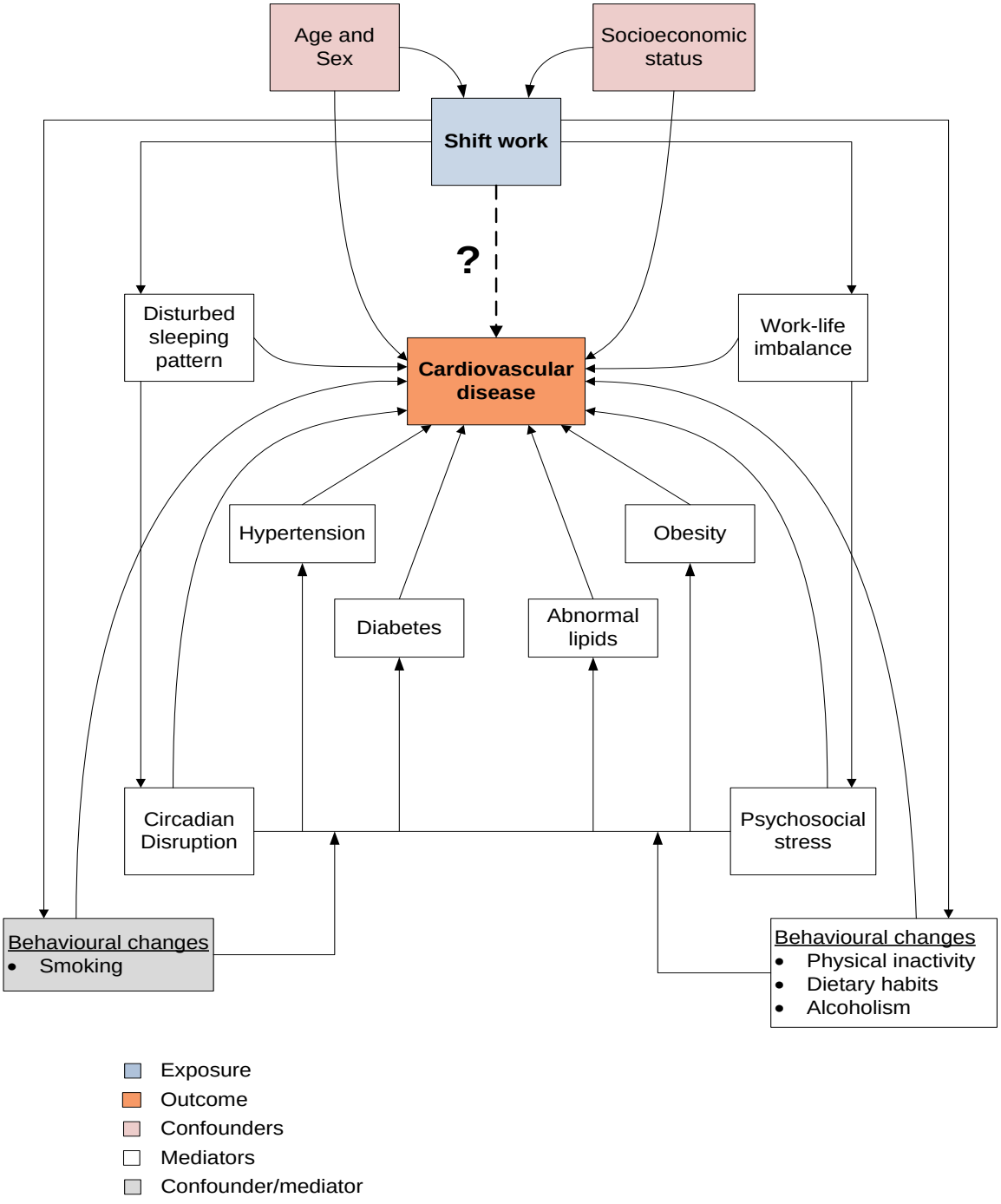
9.2 Mechanisms underlying the cardiovascular effects of shift work

Shift work is associated with various physiological and psychological changes. Figure 1 illustrates the pathways by which shift work potentially affects cardiovascular risk. Most of these have been discussed earlier. Circadian rhythm is also an important predictor of cardiovascular risk.

Circadian rhythm is an internally driven rhythm that governs production of hormones including melatonin, cortisol, prolactin and growth hormones, as well as various other functions (e.g. core body temperature, blood pressure and sleep-wakefulness) during the 24 hours of a day.[18] The suprachiasmatic nucleus of the hypothalamus is the main site that maintains the circadian rhythm of the body. Various other biological clocks are located locally in different tissues that are responsible for regulation of rhythms at the tissue level.[120] Circadian control maintains normal physiology and so circadian disruption may lead to disease. The risk of acute coronary and cerebrovascular episodes, such as angina and intracerebral haemorrhage, is pronounced in the morning hours.[121, 122] The results of a meta-analysis suggest that the risk of onset of acute myocardial infarction

is 40% higher in the morning hours and that of sudden cardiac death is 1.3 times higher.[123] About 9% cases of acute myocardial infarctions are attributed to the circadian wave.[123]

Figure 1. Underlying mechanisms for cardiovascular disease in shift workers



Light is a major synchronizing factor for circadian rhythm in humans.[124] Shift work leads to circadian disruption because of rapidly changing and conflicting light-dark exposure and activity-rest behaviour. The effects of circadian disruption as reported in studies that used various animal models include weight gain and altered hormonal metabolism.[125] In addition, cardiovascular risk factors such as diabetes and hypertension are likely to occur after circadian disruption.[126, 127] A recent animal study conducted by Martino et al. demonstrated that circadian misalignment alters *per2* and *bmal* cellular clock mechanisms causing reduced contractility, increased blood pressure and myocardial fibrosis.[128] This study also observed conversion of these mechanisms back to normal with resynchronization of circadian rhythm. A single shift work type that causes the least chronodisruption has not been identified yet.[129] However, night and rotating types of shift work may be associated with a higher risk than others.[67] As well, disturbed sleep and insomnia, which are likely with rotating and night shift work types, are associated with a higher risk of myocardial infarction.[24, 130]

9.3 Cardiovascular outcomes of interest

In order to draw conclusions that are clinically relevant and easily interpretable, we divided the broad concept of circulatory disease as defined in the International Classification of Disease version 10 (ICD-10) into clinically relevant outcomes as follows:

a. Myocardial Infarction [ICD-10 I21-25]. This includes acute and chronic myocardial infarction along with its attendant complications (e.g. ruptured chordae tendinae and others). Both fatal and non-fatal infarctions are included. In most studies, these were classified using the World Health Organization definition of myocardial infarction, based on typical symptoms, cardiac biomarker changes and electrocardiographic changes.

b. All coronary events [ICD-10 I20-125]. This includes angina and myocardial infarction along with complications as a result of infarction. Under this group, we included both morbidity (e.g. hospitalization) and death due to any of these events.

c. Coronary deaths [ICD-10 I20-I25]. This included deaths due to coronary disease as determined by death certificate, autopsy or medical records.

d. Ischemic stroke [ICD-10 I63]. This includes cerebral infarction due to occlusion of cerebral arteries arising as a result of embolism or thrombosis. Both fatal and non-fatal ischemic strokes were included under this definition. In studies with this outcome, strokes were confirmed using a combination of neuroimaging and/or autopsy results.

e. Cerebrovascular deaths [ICD-10 I60-I69]. This includes deaths due to any cerebrovascular cause including intracerebral hemorrhage, ischemic stroke and subarachnoid haemorrhage, as defined by death certificate, autopsy, or medical records.

f. Cardiovascular events [ICD-10 I00-I99]. This includes all circulatory diseases.

g. Cardiovascular deaths [ICD-10 I00-I99]. Only deaths due to circulatory disease were included in this. For ease of clinical interpretation, we kept this group separate from the coronary events, although it should be noted that coronary deaths are one subtype of circulatory death.

h. All-cause mortality. This represents death from any cause.

10 Challenges with shift work research

10.1 Lack of randomized controlled trials

One hurdle with shift work as an exposure is that it is dynamic and dependent. It depends on more than one factor. Factors determining a shift system at any given workplace include the resources available for the shift system, demand for services provided or goods produced, and the micro- and macro-economic environment in which it is nested. Individual factors determining shift work are willingness to work in shifts and the need to be employed. A clinical trial to study long-term cardiovascular effects of shift work is not viable because allocation of shift work to workers is unethical and not pragmatic. Therefore, present evidence on the effects of shift work on health is based largely on observational studies.

10.2 Lack of animal models

Replicating shift work schedules in animals is difficult because animals cannot be trained

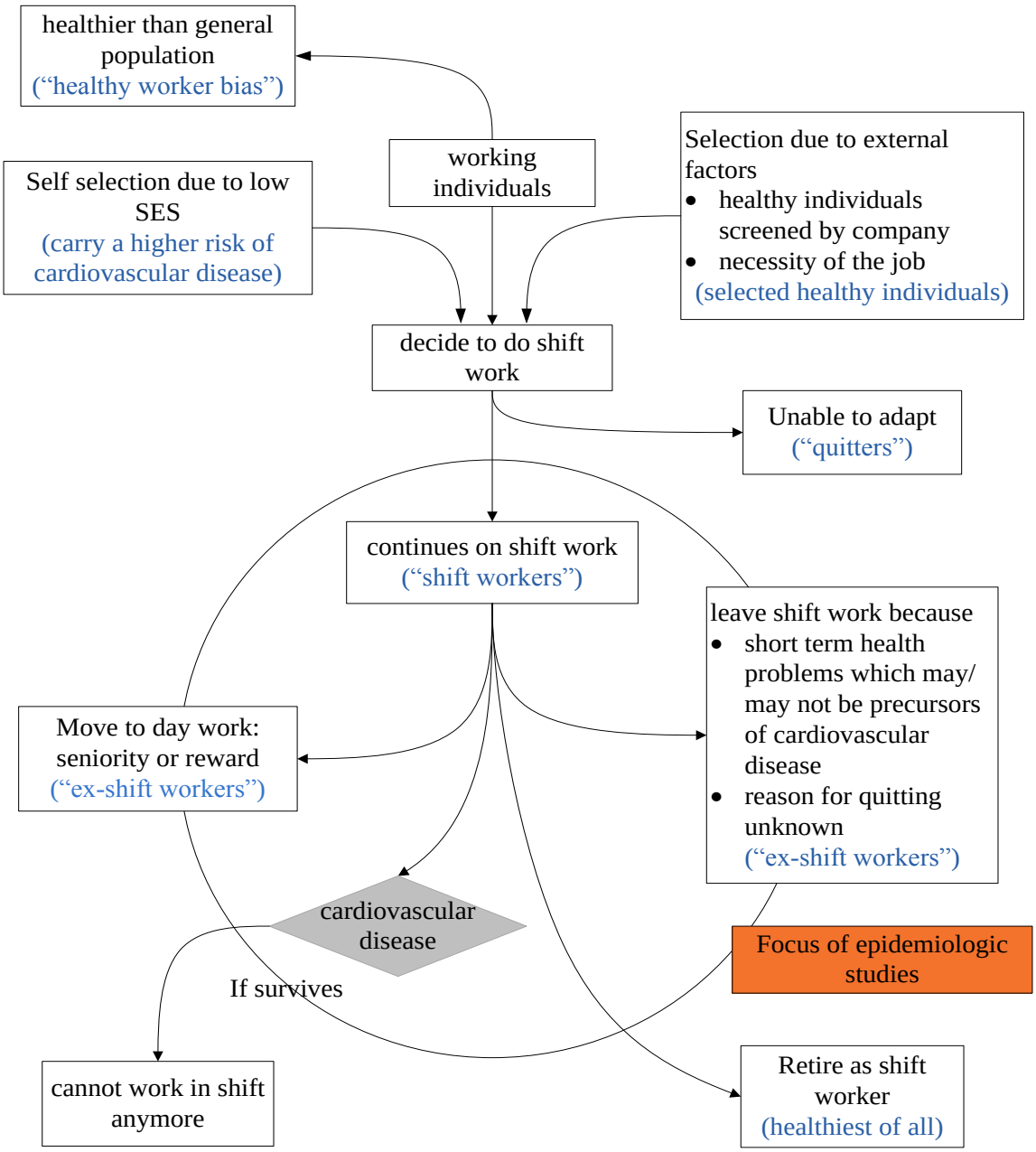
to work in shifts. Only a few animal models exist that can replicate the circadian disruption in shift workers. One such model is the Cry 1 and 2-gene knockout mouse, with resulting disruption of circadian rhythm.[78] While chrono-disruption can be recreated in the lab, the foregoing discussion pointed out that there is much more than just circadian disruption operative in shift workers. Animal models fail to capture psychosocial consequences of work-life imbalance, which may be important contributors to cardiovascular disease.[67] Despite this, the risk of vascular disease and cardiomyopathy was increased in animal models that replicated circadian disruption.[128, 131]

10.3 Selection bias in shift work studies

At the factory level, the selection of work schedule (shift work) for workers lacks an element of randomness. Factors like physical ability, willingness to work in shifts, and seniority or past job experience can influence the assignment of work schedule for any given individual. Workplaces screen individuals to select those believed to be able to handle shift work before asking them to work in shifts. Personal factors determining selection of a shift schedule by workers are need for employment and level of education. Individuals with low education and greater need for employment may be more willing to do shift work than others. For some professions involving emergency services, working in shifts is a prerequisite for the occupation involved, and hence engaged individuals become shift workers for different reasons. Selection of a worker into shift work is thus influenced by various reasons.

Some workers, who may not be sure whether shift work is tolerable to them or not, initiate shift work and leave the job after a short period of time because they cannot adjust to the working hours or job demands. These workers, whom we can term "quitters", are rarely captured in epidemiologic studies. Others, who continue working in shifts for a stipulated amount of time, are considered "shift workers" in epidemiologic studies. The balance between the health of the worker and the need to be employed, together with their educational level, determines who becomes a shift worker. This selection process leads to various biases when trying to determine the independent effect of shift work on cardiovascular disease as shown in Figure 2.

Figure 2. Challenges with epidemiologic studies on shift work and cardiovascular disease



Abbreviation: SES socioeconomic class

11 Rationale for the research

11.1 Literature to date

Multiple studies have assessed the effects of shift work on health, specifically effects on cardiovascular disease. The methods and populations vary across different studies. Study designs may be cross-sectional, crossover, case-control and cohort; endpoints vary considerably. Control groups and exposure characteristics differ considerably as well. There are disparate results and conclusions from these studies.

Only a few previous reviews have systematically synthesized the evidence on the relationship between shift work and cardiovascular disease.[12, 101, 132] These reviews have generally concluded that the risk of cardiovascular disease in shift workers is higher. One recent review, studying the effects of shift work on the risk of ischemic heart disease concluded that "a causal relationship is possible but it is … [likely] that this relationship can be explained by chance, bias or confounding."[132] Of note, the authors did not perform a meta-analysis to quantify this association. Following this review, investigators from the Nurses' Health Study cohort found that the multivariable hazard ratio of developing ischemic stroke expressed per five years of rotating shift work was 1.04 (95% confidence interval 1.01 to 1.07) suggesting a dose-response relationship between shift work and ischemic stroke.[133] Conversely, and also following this review, the adjusted hazard ratio for coronary heart disease mortality in male shift workers was reported to be non-significantly increased at 1.09 (95% confidence interval 0.82 to 1.44) by Hublin et al.[134] Hence, epidemiological evidence on the association of shift work and cardiovascular disease has accumulated with no definitive overall answer or message.

11.2 Poor methodological quality of previous reviews

Many studies have reviewed the effects of shift work on general health but not cardiovascular disease in particular. We identified ten review articles that studied the effects of shift work on cardiovascular disease.[12, 67, 101, 132, 135-140] Some of these reviews were narrative reviews (n = 6), studying specific aspects of the relationship between shift work and cardiovascular disease. For example, Puttonen et al. studied the pathways that can lead to increased cardiovascular risk in shift workers.[67] Only four reviews systematically studied the effects of shift work with the primary objective to characterize the association between shift work and cardiovascular disease.[12, 101, 132, 140] The very first

of these reviews was published in 1989 and the latest one was published in 2011.[12, 132] Only three reviews reported the search strategy that was used for searching relevant studies.[101, 132, 140] Reviews by Frost et al. and Jaehyeok et al. searched only in Medline, while that by Boggild and Knutsson searched Medline and National Institute for Occupational Safety And Health Technical Information Center (NIOSHTIC) databases. All reviews searched bibliographies of included studies for additional studies ("snowballing"). Only two studies looked at grey literature to obtain unpublished data.[12, 101]

The Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) guidelines encourage review authors to assess all included studies for methodological quality or risk of bias.[141, 142] Only two out of four reviews assessed individual studies for risk of bias or methodological quality.[12, 101] The methods of assessment used in these reviews were not validated. Only the review by Frost et al. reported the total number of titles screened and the process of article screening; however, reasons for exclusion of studies were not explicitly mentioned. Whereas the review by Kristenen et al. did not specify eligibility criteria at all, the review by Frost et al. was the only article that had well-defined and clearly reported eligibility criteria. However, a selection criterion for this review was that the study had to be published in a peer-reviewed journal, potentially instilling publication bias. Finally, of all the reviews, only the review by Frost et al. reported specifically those items that were abstracted from each study. Thus, the review by Frost et al. can be considered the most comprehensive review to date. Our literature search shows that relevant articles studying cardiovascular implications of shift work have been published after this review.[130, 133, 134, 143]

Except for the review conducted by Jaehyeok and colleagues, no other study has synthesized data to obtain pooled risk estimates. The latter reported a pooled risk ratio for the risk of ischemic heart disease in shift workers compared to day workers of 1.17 (95% confidence interval 1.00 to 1.37). The analysis included only eight studies. They reported significant heterogeneity (I^2 = 61%) and publication bias which attenuated the pooled risk estimate making the risk ratio insignificant (adjusted risk ratio 1.12, 95% confidence interval 0.94 to 1.33). Hence, a comprehensive systematic review is required

to synthesize the evidence in order to determine the cardiovascular associations of shift work.

11.3 Implications from present research

We will comprehensively search all literature sources and, through appropriate statistical methods, quantify the association between shift work and cardiovascular disease. The results will be important for policy-makers and occupational health practitioners. Cardiovascular disease is an important cause of morbidity and mortality, having serious economic consequences for the health care system and for individual workers (death, disability, premature retirement or work modification, etc.). Contingent on our findings, this research may encourage public health authorities and policy-makers to take appropriate steps to protect and promote the health of shift workers.

12 Research questions

12.1 Primary question

Are shift workers at higher risk than day workers for adverse cardiovascular outcomes such as myocardial infarction, coronary events and ischemic stroke?

Hypothesis

Our primary hypothesis is that the risk of myocardial infarction, coronary events and ischemic stroke are significantly associated with shift work, even after adjustment for potential confounders.

12.2 Secondary questions

Are shift workers at higher risk than day workers for cardiovascular mortality?

Hypothesis

We hypothesize that death due to cardiovascular disease, but not all-cause mortality, will be higher among shift workers, even after adjustment for potential confounders.

12.3 Exploratory analyses

a) Which type of shift work, if any, is worse than others when considering the risk of coronary events?

Hypothesis

We hypothesize that night work and rotating shift work will have the highest associative risks for coronary events because they both imbue the highest degrees of work-imbalance and circadian disruption.[67, 144]

b) Does a dose-response relationship exist between shift work and cardiovascular disease?

Hypothesis

Previous reviews have not attempted to quantify the dose-response of shift work on cardiovascular disease. We will seek to answer this question to determine whether such an association exists and to characterize its degree. According to Bradford Hill's criteria for causality, dose-response is an important component criterion in assessing potential causality between exposure and disease.[145]

Chapter 2 Methods

1 Overview

We conducted this review in accordance with the Meta-analysis of Observational Studies (MOOSE) recommendations and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (completed checklists in Appendices A and B).[142, 146] We focused our review on observational studies of shift work and cardiovascular events or mortality. We paid particular attention to dose-response gradients, ex-shift worker analyses, and sources of heterogeneity for cardiovascular risk.

2 Study eligibility criteria

We developed our study eligibility criteria in consultation with content experts and epidemiologists. We kept our selection criteria as broad as possible. We pilot-tested these criteria on initially identified studies using a standardized eligibility rating form (Appendix C). Four investigators reviewed the form for its utility and effectiveness. We prespecified the following eligibility criteria:

- Exposure group: The study sample must include a defined group of shift workers (the "exposure group"). These participants may engage in evening shifts, night shifts, rotating shifts, split shifts, on call shifts, casual shifts, mixed shifts or irregular shifts.

- Comparison group: The study sample should also include a control comparison group comprising either day workers or a general population sample from the same country as the exposure group.

- Outcome: Studies must report cardiovascular events or death. Cardiovascular events could include angina, myocardial infarction, cardiac arrest, heart failure, cardiovascular death or stroke. Death endpoints included all-cause mortality, cardiovascular mortality, cerebrovascular mortality or coronary mortality. We excluded studies with self-reported cardiovascular complaints or symptoms without a physician-verified diagnosis, hospitalization or death as the outcome of interest.

- Analysis and reporting of a risk estimate for shift work and outcomes of interest: We selected studies that reported a risk estimate and confidence interval, standard error or p value, or sufficient numeric data to compute these statistics. To calculate risk estimates from raw data, the latter could include dichotomous event data in the exposure (shift work) and comparison groups; incidence rates or cumulative incidence in exposure and control groups; a Kaplan-Meier survival graph with two or more curves; or observed and expected numbers of events. Risk estimates could be reported as risk ratios, relative risks, odds ratios, hazard rate ratios, rate ratios, incidence density ratios, standardized mortality ratios, standardized morbidity ratios or standardized hospitalization ratios.

3 Literature search

To identify all pertinent reports, we developed a comprehensive search strategy in collaboration with a research librarian and a medical informatics specialist. We developed our primary strategy for use in the Medline database and then adapted it to all other databases. We used combinations of free text key words as well as medical subject headings to formulate the search strategy in Medline, with analogous terms in the other databases.

We pilot-tested this strategy to assess its yield of highly relevant studies and then used additional search terms from identified studies to refine the search in an iterative fashion. In the pilot phase, we identified 94 relevant hits among 3247 articles. A final list of search terms for shift work and cardiovascular disease in Medline is presented in Table 2. The full strategy is elaborated in Appendix D.

Due to limited support for translation, we restricted our search to English language articles. Language limits can impose information bias; however, we found that most articles on shift work written in a regional language were also published in the English language international literature, thus reducing this potential bias.[147-149] We applied additional limits to restrict our search to adult populations, which form the vast majority of working samples in the occupational literature. We also excluded animal experiments.

As noted above, we adapted the Medline-based search strategy to other databases (specifically EMBASE, ProQuest, Scopus, Web of Science, Google Scholar and BIOSIS Previews). All searches were conducted from the inception date of each database and updated regularly until January 1, 2012, using customized weekly auto-alert emails forwarded to two investigators.

We used supplementary search methods after identification of an initial list of eligible studies. For example, we manually screened the bibliographies of eligible studies and relevant systematic reviews for additional relevant articles (this technique is commonly known as "snowballing").[150] We searched the grey literature by contacting experts in the field and screening conference proceedings and indices of occupational health journals for additional titles, as well as perusing our own personal files.

Table 2. Selected keywords and medical subject headings employed in the Medline search strategy

Search topic	Key words	MeSH terms
Shift nature of work	alternating, atypical, circadian, ergonomic, evening, extended, irregular, night, on-call, overnight, rotating, shift, unconventional	chronobiology disorders, circadian rhythm, work schedule tolerance
Work	call, duty, float, hours, roster, schedule, system, work	personnel staffing and scheduling
Cardiovascular outcomes	angina, arrhythmia, arterial occlusion, arterial obstruction, arteriosclerosis, asystole, atherosclerosis, cardiac, cardio, CAD, CHD, CHF, CVA, cerebral, cerebrovascular, coronary, heart, heart failure, IHD, infarct, ischemia, MI, myocardial, stroke, thrombotic, vascular	cardiovascular agents, cardiovascular diseases, cardiovascular system, cerebrovascular disorders
Mortality and mortality	actuarial, Cox model, dead, death(s), die, dying, fatal, hazard model, Kaplan-Meier, Kaplan Meier, lifetable, life table, lethal, morbidity, mortality	actuarial analysis, cause of death, death, death certificates, fatal outcome, hospital mortality, life expectancy, life tables, morbidity, mortality, sudden death, vital statistics

Abbreviations: CAD coronary artery disease, CHD coronary heart disease, CHF congestive heart failure, CVA cerebrovascular accidents, CVD cardiovascular disease, IHD ischemic heart disease, MeSH medical subject heading, MI myocardial infarction.

4 Article screening

We used Reference Manager Version 12.0.3 (Thomson Reuters, California, USA) to download and manipulate all citations in the review, including the removal of duplicate references. Two reviewers (MV and DH) independently screened the title, abstract and keywords of each citation for potential relevance. When any ambiguity was present, we obtained the full text of the publication. As a quality control, MV performed an audit of the primary screening by re-screening 400 randomly selected titles, blinded to the results of primary selection. This quality control helped to select the studies that may have been missed; however, only 2 additional studies were added after the audit, neither of which was ultimately eligible for inclusion. Both reviewers independently screened all retrieved studies against the prespecified eligibility criteria using the standardized rating form (Appendix C).

For separate publications that included overlapping or duplicate study populations, we used a decision rule to select the most pertinent study for our meta-analysis, with the goal of avoiding multiplicity of data.[151] Specifically, we selected studies with the following desired characteristics (in the following order of preference): a) longest duration of follow-up; b) highest number of confounding variables adjusted for in the calculation of shift work-outcome associations; c) least risk of bias (e.g. prospective cohort studies were preferred to nested case-control studies from the same population); and d) largest sample size. We resolved differences in adjudication by consulting with a third reviewer (Dr. Marko Mrkobrada). We calculated Cohen's kappa with 95% confidence interval for the final study adjudication.[152] Although the use of the kappa statistic is deemed controversial by some authors, it has many desirable properties including accounting for chance agreement and the ability to construct confidence intervals.[153] The values of kappa were interpreted as follows: 0.40 to 0.59 reflect fair agreement, 0.60 to 0.74 reflect good agreement, and ≥ 0.75 reflect excellent agreement.[154]

5 Data abstraction

We developed a comprehensive data abstraction form in Microsoft Excel 2010 containing citation information; study design, population and setting; exposure and outcome details;

methodological quality; and information on analytical models for the statistical analyses (Appendix E). We randomly selected seven studies to pilot-test and refine the form. Two reviewers abstracted the data independently and in duplicate, with crosschecking of discrepancies against the original reports. We clarified missing information directly with study authors. When authors did not respond, the information was considered unavailable.

We abstracted the following variables from each study: study design (e.g. "prospective cohort"); study period (beginning year of subject accrual); inclusion and exclusion criteria for the study population; population characteristics including demographic information (mean age, proportion of females, socioeconomic status, marital status, education and smoking status, where reported); details on exposures (definitions of shift work, duration of exposure to shift work, sources of information for the exposure data); details on outcomes (type and number of outcomes, definitions, sources of information for outcome data); details on confounders; risk estimates for all outcomes of interest (both crude and adjusted); follow-up duration (for longitudinal studies); tests of ex-shift worker risk, dose-response gradients and subgroup analyses; total number of reported analyses; funding sources; and the presence of selective reporting bias. We deemed selective reporting bias to be present when a study did not report outcomes or analyses prespecified in the methods of the paper (for example, suppressing them because they were considered statistically non-significant).[155]

6 Assessing bias in individual studies

We used the Downs and Black scale to evaluate the risk of bias in the included studies, with bias estimates displayed graphically using the Cochrane risk of bias graph.[141, 156] A systematic review by Deeks et al. identified 182 quality assessment tools for assessing the quality of non-randomized studies.[157] Of these, Deeks et al. considered fourteen tools to be the 'best tools' according to their prespecified criteria, but they deemed only five of them to be suitable for systematic reviews. Only two tools, the Newcastle-Ottawa scale and the Downs and Black scale, distinguished between what was conducted as a part of the study and what was reported, differentiating between methodological quality and the

quality of reporting of a study.[156, 158, 159] We selected the Downs and Black scale for our purposes because it has excellent test-retest reliability (r = 0.88), inter-rater reliability (r = 0.75) and internal consistency (Kuder-Richardson 20 r = 0.89).[156] It also provides a numeric score for overall study quality that is easy to interpret.

The Downs and Black scale is composed of 27 items subdivided into five components: reporting, external validity, internal validity, confounding and power (Appendix F). The answers to each item are scored from 0 to 1, except for item 5 on reporting confounding distribution across comparison groups (maximum score of 2) and item 27 on statistical power (maximum score of 5). For the item on reporting confounding distribution, *a priori* we defined age, sex, socioeconomic class and smoking as our confounders of interest, given their pre-eminence as confounders in the occupational health literature (see Chapter 1).[104, 160, 161] Only studies that reported the distribution of at least four confounders of interest among the comparison groups could attain the maximum score of 2 points for this item.

It should also be noted that the Downs and Black scale contains three items that assess randomization, subject blinding and allocation concealment, none of which are typically applicable to observational studies. We therefore adapted the scale by removing these three items; a study with maximal quality would therefore score 29 points.

7 Exposure of interest

In the primary analysis, any form of shift work was considered the exposure of interest. When available, details of shift work (e.g. type and duration) were considered in secondary analyses. When a given study reported risk estimates for more than one type of shift work, we selected for the primary outcomes the risk estimate that was based on largest number of workers.

8 Outcomes of interest

Given the range and diversity of reported outcomes, we preselected three clinically important outcomes for the primary analysis: myocardial infarction, all coronary events (namely coronary-related hospitalizations, myocardial infarctions and/or coronary

mortality) and ischemic stroke. Secondary outcomes were all cardiovascular events, coronary mortality, cerebrovascular mortality, cardiovascular mortality and all-cause mortality. The endpoint of "all cardiovascular events" was typically defined using International Classification Disease subcodes representing all circulatory diseases. We found no reports of hemorrhagic stroke or heart failure in relation to shift work; therefore, these outcomes were not considered further.

9 Statistical analysis

We computed summary statistics with proportions and 95% confidence intervals (CIs) for categorical variables, and means with standard deviations for continuous variables (most studies reported means rather than medians, and Question 7 in the Downs and Black scale addressed whether studies tested for a normal distribution). We extracted unadjusted and fully adjusted risk estimates and 95% CIs for all outcomes of interest and for each type of shift work from each study independently and in duplicate. We conducted an audit to ensure that no errors were made in the abstraction and data entry of risk estimates and other variables.

For the primary analysis, we included only fully adjusted risk estimates, with the exception of two studies that only presented crude estimates.[162, 163] When a study reported risk estimates stratified by sex and/or work type (e.g. white collar vs. blue collar), we combined these estimates using a fixed effects model to obtain a single study-specific estimate for that study's sample.[164] We then combined all risk estimates by outcome type to obtain pooled outcome risk ratios (RR) using generic inverse variance random effects models.[165] We assumed similarity between different types of risk estimates (e.g. odds ratio versus relative risk) because events of interest were rare.[166]

We used random effects models since studies typically differed in sampling mix and type and intensity of shift work exposure.[167, 168] We believed that the studies selected represent a sample from a larger population of the studies and that the risk estimates follow a distribution. The random effects model will determine the mean of this distribution. We used the generic inverse variance statistical model because it allows integration of adjusted risk ratios without the need to know dichotomous outcome data.[169] Higgins' I^2

values were used to assess the degree of statistical heterogeneity between the studies.[170] The I^2 statistic is the proportion of observed dispersion that is real rather than spurious. It is expressed as a ratio with a range of 0 to 100%. As a general rule, $I^2 < 25\%$ represents little evidence for heterogeneity; $I^2 = 25$ to 50% represents moderate heterogeneity; and $I^2 > 50\%$ represents notable heterogeneity.[171] We performed all analyses using Comprehensive Meta Analysis Version 2.0 (Inglewood, NJ). We deemed two-tailed *P* values < 0.05 to be statistically significant.

9.1 Sensitivity analyses

To assess for publication bias, we used the Duval and Tweedie's trim and fill method to obtain publication bias-adjusted estimates.[172] This method of bias assessment calculates the pooled risk ratio adjusted for the effects of publication bias by removing or imputing studies such that funnel plots become symmetrical. This method therefore both assesses the presence or absence of publication bias and measures the extent to which publication bias has altered the observed risk ratio.[172, 173]

In general, the quality of evidence from observational studies is considered to be lower than that deriving from randomized trials. This is due to the inability of observational studies to completely control for confounding.[174] To identify the extent to which confounding affects the association of shift work with cardiovascular disease, we conducted sensitivity analyses by separately pooling adjusted and unadjusted risk ratios in the subset of studies that reported both types of estimates. Thus, we obtained an additional pair of risk ratios for each of the three primary outcomes: unadjusted and adjusted myocardial infarction, ischemic stroke and coronary events. The pooled adjusted risk ratio will differ substantially from the pooled unadjusted risk ratio if measured confounding significantly affects the association between shift work and cardiovascular disease.[175]

9.2 Secondary analyses

Secondary endpoints

We considered cardiovascular events, coronary mortality, cerebrovascular mortality,

cardiovascular mortality and all-cause mortality as secondary outcomes. We obtained pooled risk ratios for these outcomes using the generic inverse variance random effects models and synthesizing adjusted estimates only.

Heterogeneity

Because one of the primary outcomes indicated substantial statistical heterogeneity (specifically coronary events), we explored variation in this outcome across studies using univariate random effects meta-regression analysis.[169] We performed this meta-regression using unrestricted maximum likelihood estimation. This method was chosen over other techniques because it yields a conservatively wide confidence interval of the estimated beta coefficient and thus imposes caution in the extrapolation of results to future studies or participants.[176, 177] We did not attempt to adjust for multiple comparisons as all analyses were confined to the endpoint of coronary events and were considered exploratory in nature.[178]

Using the meta-regression analysis, we assessed the impact of the following factors on the log risk ratio for coronary events:

1) Study region. We considered studies conducted in Europe, the most commonly represented region by far, as the reference category and studies from all other regions were considered as the 'other' category (specifically Asia or the United States, for which there were relatively few studies).

2) Accrual start. We abstracted the year participant accrual began for each study. In the rare instance when a study did not report year of accrual we deducted five years from the date of publication and imputed the resulting year as an estimate of accrual start.

3) Length of follow-up. We obtained the maximum duration of follow-up (in years) for both retrospective and prospective cohort studies. We restricted this analysis to cohort studies only.

4) Sample size. We meta-regressed the total effective sample size used to obtain the risk estimate for each study.

5) Proportion of shift workers. For studies that reported the number of shift workers and day workers, we obtained the overall percentage of shift workers in each study sample.

6) Age and sex. All other factors being equal, males are at a higher risk for cardiovascular events than females.[179] In addition, the majority of shift workers are male, with the exception being the nursing profession and health care aids.[19, 180] We modelled sex distribution as the percentage of females in the study population. The risk of cardiovascular disease increases with increasing age and thus we also modelled the mean age of the study population to study its effect on the risk estimate.[181] When mean age was not available we used (in order of preference) median age (if available) or the midpoint of the age range of the study participants as an approximation to median age.

7) Job type. Blue collar workers may constitute a sub-population with different cardiovascular risk factors than white collar workers.[182] Job types varied across studies and thus we modelled job type as the percentage of blue-collar workers in the study population.

8) Shift work schedule. Rotating shift work was the most commonly studied type of shift work. This meta-regression explored heterogeneity between studies by modelling shift work schedule as rotating versus all other schedules (e.g. fixed night shifts, etc.).

9) Event type. We analysed whether estimates differed for studies that reported only MI as the principal type of "coronary event" as opposed to those that studied other coronary end points as well (e.g. coronary mortality or coronary hospitalizations).

10) Data source for outcome ascertainment. *Primary* data sources included subject interviews, census data, direct patient contact/tracing, clinical registries or single-site hospital records while *secondary* data sources were administrative databases

or non-clinical automated registers. This regression analysis was modelled using a binary covariate (primary vs. secondary data source).

11) Sample risk. Sample risk was defined as the overall event rate in a cohort (hence we restricted this analysis to cohort studies only). The event rate was calculated as the total number of events in the entire cohort divided by the total person-years of follow-up.

12) Type of control group. Studies that used the general population as a control group typically included both shift workers and day workers in the control group. Thus, the estimates from such studies may be biased towards the null because of control group contamination. In this meta-regression, we contrasted studies which used general population control groups versus the more frequently used day worker control groups.

13) Adjusting for confounding. Observational studies cannot control for all potential confounding. In two separate meta-regressions, we modelled whether studies adjusted for two specific confounders frequently emphasized in the peer-reviewed occupational literature: socioeconomic status and smoking. Furthermore, as a crude measure of the degree of potential confounding adjusted for, we meta-regressed the number of distinct confounders adjusted for in each study.

14) Time dependence. We classified studies into those that involved a time component in the denominator when calculating the risk of cardiovascular disease (typically longitudinal cohort studies reporting hazard rate ratios) and those that did not (typically cohort or case-control studies reporting odds ratios, relative risks, or standardized mortality ratios).

15) Methodological quality. We modelled the Downs and Black score for each study as a proportion of the total score possible (29 points).

16) Study power. We calculated study power using standard formulas as 1-β error for each study and modelled this as a continuous variable.

17) Duration of shift work. Finally, we performed meta-regression using the median duration of shift work in each study as a predictor variable. We used the mean duration of shift work for studies that did not report median duration.

Subgroup analyses: study design

A prospective cohort study is considered methodologically stronger than a retrospective cohort study or a case-control study because the former assesses exposure at baseline and follows participants prospectively over time to assess the outcome. Therefore, a prospective cohort study replicates the natural sequence of disease occurrence i.e., from exposure to outcome. We explored how the observed effects of shift work on primary outcomes changed across different study designs (prospective cohort, retrospective cohort and case-control studies) by undertaking subgroup analyses. Among the primary endpoints, these analyses were only possible for myocardial infarction and coronary events because only two studies were identified for ischemic stroke.

Subgroup analyses: shift work schedules

To determine the effects of different shift work schedules on coronary risk (which was the most commonly reported study endpoint and the only heterogeneous primary event), we obtained separate summary risk estimates for each shift work schedule. The following types of shift work were considered: evening work, night work, mixed shifts, rotating shifts and unspecified or irregular shifts. We performed no test of heterogeneity across schedule types as doing so would have caused control group duplication (i.e. individual studies which reported multiple risk estimates for different types of shift workers used the same control group).

Subgroup analyses: dose-response assessment

These analyses again focused on the shift work-coronary event association. Unfortunately, years of shift work exposure were categorized using markedly different cut-points across different studies. To supplement our meta-regression of median duration of shift work, we performed subgroup analyses by first recategorizing study-reported duration subsets into 5 ordered categories: very low, low, medium, high, and

very high (in the same order of categorization of the original studies). We dropped the 'medium' category for studies that did not report five categories of shift work. Estimates for each of the recategorized groups were pooled as five separate subgroup analyses. Again to avoid control group duplication, we did not perform a statistical test of trend.

Ex-shift worker analysis

We calculated the pooled adjusted risk ratio of coronary events for ex-shift worker groups compared with control groups using the random effects generic invariance method. We undertook this analysis to explore the effect of cessation of shift work exposure. As previously described, reasons for leaving shift work are multiple and often unknown, but may potentially relate to disease-associated disability.[183]

10 Overall quality of evidence

Both reviewers (MV and DH) collaboratively assessed the overall quality of evidence for the three primary outcomes using the GRADE approach.[174] It is important to remember that quality of evidence is not the same as risk of bias in individual studies. In the GRADE framework for systematic reviews, the ratings of quality of evidence reflect the extent to which synthesized estimates of effect are believed to be correct.[184] We used the suggested GRADE summary of findings table for displaying our results.

Chapter 3 Results

1 Study selection

We identified 20,756 records through all search strategies. Of these, we removed 8,406 duplicate records, leaving 12,350 unique records for title, abstract and keyword screening. After relevance screening, we discarded 12,204 records as unrelated to the research question; we retrieved the remaining 146 papers in full for review.

We found 35 studies that satisfied the prespecified eligibility criteria (κ for the two independent reviewers 0.78, 95% confidence interval 0.66 to 0.90). We excluded the remaining 111 studies for following reasons: no data on shift work exposure (n = 40); no data on outcomes of interest (n = 25); reviews, editorials, or news articles (n = 31); absence of comparison (or control) group (n = 2), insufficient data to calculate a risk estimate (n = 1); design paper (n = 1); or interventional study design (n = 1). We excluded one study, which included hypertension in the definition of coronary events.[63] We further excluded nine studies with overlapping or duplicate study populations based on our prespecified decision rule to avoid multiplicity of data.[136, 185-192] However, we retrieved these studies to obtain additional methodological information during the data abstraction phase.

The selection process is depicted in Figure 3 (*please find the figures and tables for this chapter appended at the end of the chapter on pg. 54*). We also obtained unreported risk estimates from two Norwegian researchers (Drs. Lars Laugsand and Imre Janszky) on the association of shift work with myocardial infarction in the Nord-Trøndelag Health Study (HUNT study), allowing us to integrate their recently published report on myocardial infarction and working conditions.[130]

We identified most studies in the review from initial searching of electronic databases (n = 34). We identified only one study through weekly electronic search updates.[130] The 35 studies included in the systematic review represented 34 unique datasets. The study by Knutsson et al. published in 2004 reanalyzed the data from Taylor and Pocock (originally published in 1972).[193, 194] These two studies will be considered as one study hereafter.

2 Study characteristics

Most studies were conducted in Europe (n = 26), with relatively few in Asia (n = 5) or the United States (n = 3). We identified no Canadian study meriting final inclusion. Other study characteristics are contained in Table 3.

2.1 Study size

The included studies comprised 2,011,935 participants. We noted that two sets of studies used the same or somewhat overlapping study populations. These studies were conducted by Brown et al. and Kawachi et al. (the United States Nurses' Health Study cohorts); and by Taylor and Pocock and Taylor et al. (British occupational cohorts).[133, 193, 195, 196] The studies in each set reported different outcomes of interest and employed different methods of data analyses. Therefore, we retained these studies separately in the review. For calculating the total number of participants included in the review, we selected the study with the larger sample size for these two study pairs. Sample sizes of the included studies varied from only 94 participants in the matched case-control study by Fukuoka et al. to 958,096 participants in the study by Alfredsson et al., which used a census-based population of employed individuals in five Swedish counties.

2.2 Population characteristics

The inclusion and exclusion criteria varied among studies included in the review (Table 3 on pg. 55). Only 12 studies (35%) excluded individuals who had a history of cardiovascular disease at baseline. All studies included adult populations (over 16 years of age), except for Karlsson et al., which included a small minority (n = 175, 3% of the total sample) between the ages of 10 and 14 at study entry. Four studies did not specify an upper limit of age of participants[193, 197-199] and three studies had no data on the age of participants.[196, 200, 201] Most articles reported associations of shift work and outcomes in male populations (65%); some studied a mix of male and female populations (26%), while a few studied only female populations (9%).

2.3 Exposure characteristics

The definition of shift work varied across studies (details in Table 4 on pg. 61). Six studies (18%) reported no details on the type of shift work evaluated or the overall definition of shift work.[199, 202-206] The data sources for exposure ascertainment differed across studies: company records (n = 12), questionnaires or interviews (n = 19), or occupational survey databases or administrative data (n = 3). Shift work types included mixed shift work (n = 11), rotating work (n = 10), night work (n = 9), unspecified or irregular work (n = 8), and evening work (n = 4). Seven studies (21%) tested the association between more than one type of shift work and outcomes.[134, 143, 201, 205, 207-209] The prevalence of shift workers varied from 11% to 78% (mean 36%, standard deviation 22%) across studies.

2.4 Control group characteristics

Most studies (n = 30) used day workers as the control group while four studies used a more general population of employed workers from the same geographical region as a control group.[193, 200, 209, 210]

2.5 Outcome characteristics

Details of outcomes reported in the included studies are presented in Table 5 (pg. 65). The types of data sources for outcome ascertainment were distributed evenly across studies: 16 studies used *primary* data sources (interview, census data, direct patient contact/tracing, clinical registries or individual hospital records) and 18 used *secondary* data sources exclusively (administrative databases or non-clinical registers). Most studies used International Classification of Diseases coding for defining cardiovascular outcomes. Only one study recorded outcomes based on self-reported physician diagnoses of myocardial infarction.[198]

2.6 Study designs

Included studies were either prospective cohorts (n = 11), retrospective cohorts (n = 13), or case-control studies (n = 10). Of the 10 case-control studies, five were nested case-

control studies[161, 201, 208, 211, 212] within a larger cohort and five were non-nested, matched case-control samples.

2.7 Follow-up (cohort studies only)

The duration of follow-up varied among studies. The study with longest follow-up was Karlsson et al.[213] This study recorded the mortality of a cohort across 50 years from January 1, 1952 to December 31, 2001 by linkage to the National Cause-of-Death Register. Alfredsson et al. had the shortest follow-up of one year only.[210]

3 Risk of bias within studies

The methodological quality of included studies was determined by using the Downs and Black checklist. The median score of study quality for the included studies expressed as a percentage was 60% (interquartile range, 18%). The risk of bias graph is presented in Figure 4 (pg. 70). The most common deficiencies in the included studies were lack of data on contamination of comparison groups (due to failure to report exposure over multiple time points), and failure to report all types of adverse cardiovascular events potentially related to shift work. Most studies reported a well-defined hypothesis or objective, described outcomes of interest clearly, and used validated outcome measures. Of 30 studies included in the meta-analyses of primary outcomes, 19 studies (59%) were not sufficiently powered (< 80%) to detect a clinically relevant difference while for 4 studies (12%),[130, 134, 143, 205] post-hoc power could not be calculated due to lack of numeric data necessary for such calculation.

Only three studies (9%) exhibited evidence of selective reporting bias.[203, 205, 210] These studies assessed the association of various work-related exposures (including shift work) with selected cardiovascular outcomes, but did not report results of several of these exposure-outcome associations when they were not statistically significant.

4 Results of individual studies

The results from individual studies are listed in Table 6 (pg. 71) and displayed in forest plots of meta-analyses of each cardiovascular outcome in Appendix G. All except two

studies[162, 163] accounted for one or more confounders through restriction, stratification, matching, or regression analysis in shift work-outcome analyses.

5 Primary analyses

We abstracted 6,598 myocardial infarction, 17,359 coronary events and 1,854 ischemic strokes from 10, 28 and 2 studies, respectively. In the pooled random effects analyses, shift work was associated with an increased risk of myocardial infarction (risk ratio 1.23, 95% confidence interval 1.15 to 1.31), all coronary events (risk ratio 1.24, 95% confidence interval 1.10 to 1.39) and ischemic stroke (risk ratio 1.05, 95% confidence interval 1.01 to 1.09, Figure 5). Statistical heterogeneities for the pooled analyses (I^2 value) were 0%, 85% and 0%, respectively, for myocardial infarction, coronary events and ischemic stroke. Of note, only three studies (11%) reported that shift work was associated with a decreased risk of coronary events; however, these estimates were statistically non-significant.[143, 160, 211]

6 Sensitivity analyses

Publication bias was assessed by Duval and Tweedie's trim and fill method (Figures 6 and 7, pg 79). For myocardial infarction, the algorithm imputed two hypothetical studies to the left of the line representing the null effect to obtain funnel plot symmetry. The association between shift work and myocardial infarction changed only slightly (Duval-and-Tweedie adjusted risk ratio 1.22, 95% confidence interval 1.15 to 1.30). Similarly, the publication bias-adjusted risk estimate for coronary events changed only slightly (adjusted risk ratio 1.19, 95% confidence interval 1.06 to 1.34). The Duval and Tweedie method could not be applied to ischemic stroke as only two studies were included. In addition, current reporting guidelines do not recommend testing for funnel plot asymmetry in analyses involving fewer than 10 studies.[214]

Adjusted and unadjusted summary risk ratios, obtained to assess the impact of confounding on the association of shift work and the three primary outcomes, showed similar results Figure 5). For example, for those studies reporting both unadjusted and adjusted analyses, coronary events had a risk estimate of 1.21 (95% confidence interval

1.06 to 1.39) in the unadjusted analyses and a risk estimate of 1.17 (95% confidence interval 1.05 to 1.31) in the adjusted analyses.

7 Secondary analyses

7.1 Secondary endpoints

Among the secondary outcomes, a trend was observed for cardiovascular mortality (random effects adjusted risk ratio 1.14, 95% confidence interval 0.98 to 1.32, $P = 0.091$, Table 7). I^2 value for this analysis was 65%, indicating substantial heterogeneity. The risks of coronary mortality and all-cause mortality were not statistically higher among shift workers (adjusted risk ratio 1.08, 95% confidence interval 0.97 to 1.21, and adjusted risk ratio 1.04, 95% confidence interval 0.97 to 1.11, respectively). These analyses were moderately heterogeneous ($I^2 = 29\%$ and 36%, respectively). We found that the risk for cerebrovascular mortality was not statistically higher in shift workers (adjusted risk ratio 1.12, 95% confidence interval 0.89 to 1.40), and was fairly heterogeneous ($I^2 = 52\%$).

7.2 Meta-regression of shift work and coronary events

Owing to strong evidence of heterogeneity in the association of shift work with coronary events ($I^2 = 85\%$), we undertook univariate random-effects meta-regression analyses to explore whether prespecified variables could explain this variation. None of the prespecified predictors was found to be significant (Table 8).

7.3 Subgroup analyses by study design

Two prospective cohort studies, two retrospective cohort studies and six case-control studies recorded the risk of myocardial infarction in shift workers. Risk of myocardial infarction was higher in prospective cohort studies followed by retrospective cohort studies and then case-control studies (Figure 8). The association between shift work and myocardial infarction was significant for each type of study design. I^2 values were 0%, 38% and 0% for prospective cohort, retrospective cohort and case-control studies, respectively.

For coronary events, the distribution of study designs was as follows: prospective cohort

studies (n = 11), retrospective cohort studies (n = 8) and case-control studies (n = 9). Higher risks of coronary events for shift workers were recorded in prospective cohort studies followed by retrospective cohort studies and then case-control studies (Figure 9).

7.4 Shift work schedules and coronary events

The risk of coronary events was found to be significantly higher for all types of shift schedules, with the exception of evening work (Table 8 on pg. 81). Only five studies tested the evening shift work-coronary event association and therefore statistically non-significant results should be interpreted with caution. There was considerable variation, assessed by I^2 values, for each shift work schedule-coronary event association. The risk of coronary events was particularly high with night shift work (risk ratio 1.41, 95% confidence interval 1.13 to 1.76, I^2 = 36%).

7.5 Dose-response assessment for coronary events

Twelve studies (35%) measured the duration of shift work in the exposed group.[133, 134, 161, 162, 193, 195, 198, 200, 211, 213, 215, 216] Of these, eight studies (24%) undertook dose-response analyses, but for one study, the measure of statistical significance (*P* value or confidence interval) was not available even after contacting the authors.[198] The study by Brown et al. reported the dose-response relation of shift work with ischemic stroke only and thus was not included in this analysis.[133]

The relation of years of shift work, divided into five ordinal categories, with coronary events is shown in Figure 10 (pg. 84). The highest risk of coronary events was observed in the 'medium' category followed by 'high' and 'very high' categories. Thus, a linear relationship was not observed. The results for each category, however, were statistically non-significant.

7.6 Ex-shift worker analysis

The ex-shift worker analysis was reported in six studies (Figure 11 on pg. 85). Each study used somewhat different definitions to select ex-shift workers. In general, however, working in shifts for some stipulated amount of time (years or months) before

quitting shift work was required in order for an individual to be considered as an "ex-shift worker". In five studies included in this analysis, ex-shift workers went back to doing day work.[134, 160, 193, 201, 211] The study by Haupt et al. did not describe the current employment status of ex-shift workers after leaving shift work. The study by Yadegarfar and McNamee defined ex-shift workers as those who had left work altogether ("inactive workers", i.e., retired shift workers).[161] The pooled risk ratio for coronary events in ex-shift workers was 1.19 (95% confidence interval 1.01 to 1.40). The I^2 statistic for this analysis was 0%. The increased risk of coronary events in ex-shift workers may suggest adverse consequences of shift work even after cessation of the exposure. It is worth mentioning that the point estimate for ex-shift workers was slightly lower than that observed in "current" shift workers as part of the primary analysis, although the confidence intervals overlapped.

8 Overall quality of evidence

The overall evidence is summarized in Table 9 (pg. 86). In the GRADE approach, randomized trials start as high-quality evidence and observational studies as low-quality evidence.[63] However, the quality from observational studies should be rated up if there is a large magnitude of effect, evidence of dose-response gradient or if plausible confounding can increase the confidence in estimated effects.[217]

A total of 30 studies (88%) determined shift work exposure at a single point (i.e. cross-sectionally). From the point when shift work status of workers was assessed to the point of outcome occurrence, workers in both groups could have moved from day work to shift work or vice versa. However, the likelihood of shift workers leaving shift work with passing years (increasing seniority) is typically thought to be higher than that of day workers taking up shift work.[160] Despite this dilution of shift work exposure, we found statistically higher risks of myocardial infarction, coronary events and ischemic stroke among shift workers. Hence, we rated up the quality of evidence for all three outcomes. Although we could not test for publication bias for ischemic stroke, we found that the point estimates for ischemic stroke and cerebrovascular mortality in shift workers were somewhat similar. Moreover, results for adjusted and unadjusted risk estimates of

ischemic stroke were similar. We therefore did not downgrade the quality of evidence for ischemic stroke.

In summary, we found moderate-quality evidence to suggest that shift work is associated with a higher risk of myocardial infarction and ischemic stroke. The higher risk of coronary events in shift workers should be considered low-quality evidence because of significant inconsistency (I^2 = 85%).

9 Tables and figures

Figure 3. Study selection

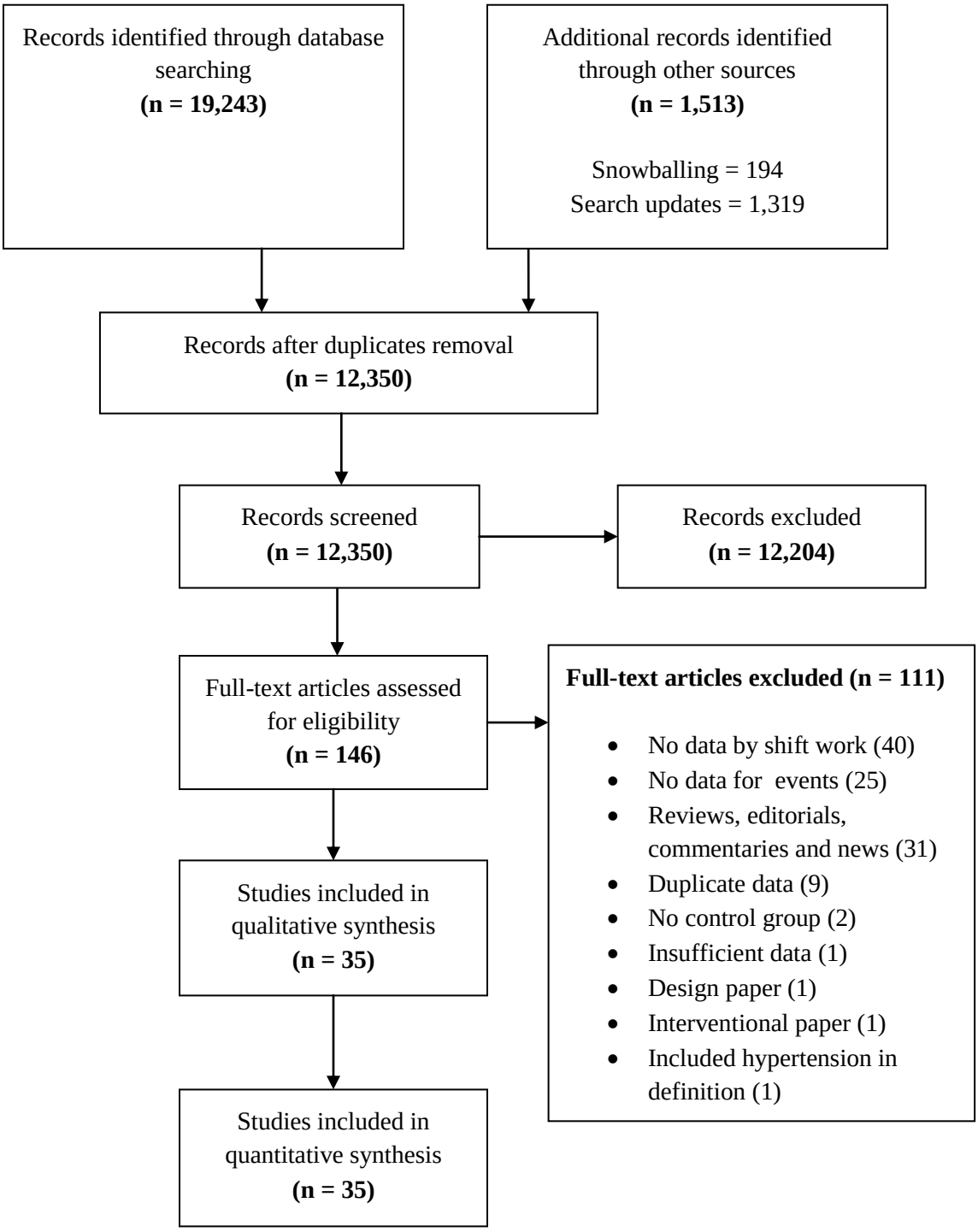


Table 3. Study characteristics

Study [ref]	Design	Setting/Data Source	Accrual period	Sample size	Inclusion criteria (Exclusion criteria)
Akerstedt et al., 2004 [218]	retrospective cohort	Swedish Living Conditions Survey	1984-1996	22,411	25-64 yr at the time of the National Survey of Living Conditions (missing data)
Alfredsson et al., 1985 [210]	retrospective cohort	Swedish census data	1975	958,096	20-64 yr, having job title in the census year, residing in selected five counties in Sweden in 1975 (farmers)
Allesoe et al., 2011 [143]	prospective cohort	Danish Nurse Cohort Study	1993	12,116	all female Danish nurses, 45-65 yr, member of Danish nurses' association (not actively employed as nurses, IHD prior to baseline survey, missing information on survey)
Babisch et al., 2005 [202]	case-control	32 major hospitals in Berlin, Germany	1998-2001	4,115	20-69 yr, residents of Berlin since at least 5 yrs preceding enrollment and lived 6 months per yr, sufficient communication & language skills (deaf patients or hearing impaired)
Biggi et al., 2008 [162]	retrospective cohort	municipal workers in Milan, Italy	1976	468	22-62 yr, employed with municipality enterprise street cleaning and domestic waste collection, residing in metropolitan area of Milan
Boggild et al., 1999 [160]	prospective cohort	Copenhagen Male Study	1970-1971	5207	all men, 40-59 yr, working at 14 companies included in the Copenhagen male study (emigrants were excluded for secondary analyses)

Study [ref]	Design	Setting/Data Source	Accrual period	Sample size	Inclusion criteria (Exclusion criteria)
Brown et al., 2009 [133]	prospective cohort	Nurses' Health Study	1988	80,108	married registered nurses, 30-55 yr at the time of first survey of Nurses Healthy Study in 1976, responded to the question on shift work in 1988 (P/H of stroke, non-Caucasian and Hispanic, missing data on one or more covariates)
Ellingsen et al., 2007 [163]	retrospective cohort	employees of a fertilizer plant in Doha, Qatar	1972-2003	2,562	all male employees at the plant (left the country at the end of their employment)
Falger and Schouten, 1992 [203]	case-control	two large hospitals in the Netherlands	1980-1983	458	men, 35-69 yr, agreed to participate. *Hospital controls* were admitted to same hospital with other acute conditions (controls who had P/H of MI)
Fujino et al., 2006 [207]	prospective cohort	survey data in Japan	1988-1990	17,649	participants of JACC study, male, 40-59 yr, full time employed or self employed (P/H of MI or cerebrovascular disease)
Fukuoka et al., 2005 [219]	case-control	five hospitals in Japan	2002	94	be mentally alert, speak Japanese, hemodynamically stable, capable of independent living, no history of advanced malignancy or debilitating illness (not employed, P/H of CHD or malignancy)
Haupt et al., 2008 [198]	retrospective cohort	survey data in West Pomerania, Germany	1997-2001	2,510	participants of SHIP, 20-79 yr at the time of survey (< 45 yr, current shift workers, uncertain information regarding shift work)

Study [(ref)]	Design	Setting/Data Source	Accrual period	Sample size	Inclusion criteria (Exclusion criteria)
Hermansson et al., 2007 [212]	case-control	survey data in Sweden	1985-2000	607	participants of VIP and MONICA population based surveys selecting participants randomly (known cancer or stroke, lack of information on shift work)
Hublin et al., 2010 [134]	prospective cohort	population-based twin cohort in Finland	1975-1981	20,142	all Finnish twin pairs of same gender born before 1958, with co-twins alive in 1975, residents of Finland (not working, missing data on work status, subjects on disability pension or retired prior to 1981)
Karlsson et al., 2005 [213]	retrospective cohort	pulp and paper workers in Sweden	1940-1998	5,442	male workers, blue-collar workers, employed for at least 6 months during study period (incomplete information about job history, > 60yr at time of employment, those who could not be traced)
Kawachi et al., 1995 [195]	prospective cohort	Nurses' Health Study	1988	79,109	participants of the Nurses' Health study, married, registered nurses, between 30-55 years (deceased, had been previously diagnosed with MI or angina or cerebrovascular disease at baseline)
Knutsson et al., 1986 [215]	prospective cohort	pulp and paper works in Sweden	1968	504	all male blue-collar workers permanently employed in the factory (born outside Sweden, younger than 20 years, P/H of IHD)

Study [ref]	Design	Setting/Data Source	Accrual period	Sample size	Inclusion criteria (Exclusion criteria)
Knutsson et al., 1999 [208]	case-control	survey data in Sweden	1992-1994	4,648	participants of Vasternorrland Infarction Project & Stockholm Heart Epidemiology Program (previously diagnosed myocardial infarction, < 45yr or > 70yr, lack of information on work schedules)
Koller, 1983 [216]	retrospective cohort	oil refinery workers in Austria	Not reported	301	randomly selected male blue-collar workers, shift workers were matched on age and years on work with day workers (those workers who could not be matched)
Laugsand et al., 2011 [130]	prospective cohort	Nord-Trøndelag Health Study (survey in Norway)	1995-1997	52,610	20-65 yr, participants of HUNT Study, responded to questionnaire on insomnia (baseline MI either self-reported or from medical records, unemployed, pensionaire, > 65 yr, doing military service, working at home [i.e. housewives] or students)
Liu and Tanaka, 2002 [220]	case-control	22 hospitals in Japan	1996-1998	705	only men. *Controls* matched from resident registers by age, sex and residence (without a job, incomplete information about working hours, and cases without matched controls and controls without matched cases)
McNamee et al., 1996 [211]	case-control	nuclear plant workers in Britain	1950-1992	934	all men, worked at least one month in the company (professional, technical and administrative staff were excluded)
Netterstrom et al., 1999 [204]	case-control	two Danish hospitals	1991-1992	252	wage earners currently employed, under 60 years

Study [ref]	Design	Setting/Data Source	Accrual period	Sample size	Inclusion criteria (Exclusion criteria)
Rafnsson and Gunnarsdottir, 1990 [200]	retrospective cohort	fertilizer plant workers in Iceland	1954-1985	603	all men hired/working during accrual period
Steenland and Fine, 1996 [201]	case-control	heavy equipment plant workers (US)	1951-1988	944	male, welders or welder helpers employed for at least 2 yr or more at any work-site included in the study (maintenance welders, flame cutters, burners, machinists, painters, foundry workers, not adequate personnel records, P/H of heart disease)
Tarumi, 1997 [206]	retrospective cohort	Japanese steel industry workers	1991-1995	9,141	≥40 years, employees of the parent company (data from females, white collar workers and that of workers from subsidiary company)
Taylor and Pocock (re-analyzed by Knutsson et al., 2004) [193, 194]	retrospective cohort	10 industrial organizations in Britain	1956-1968	8,048	all male manual workers, full time employment on 1st January 1956, born before 1920, continuously employed for at least 10 years between 1946–1968 (workers who did not fit into any work schedule category were excluded)
Taylor et al., 1972 [196]	retrospective cohort	29 industrial organizations in Britain	1968-1969	1,548	only males, employed as manual workers in same organization & same site before 1967, continuously employed without change of job or working hours for two study years 1968 & 1969 (those who transferred at any time during their employment from one system of working hours to another on medical grounds)
Tuchsen, 1993 [209]	prospective cohort	Danish survey data	1981-1984	406,969	all men in the Central Population register, 20-59 yr (male nurses and therapists, and nurse assistants and porters)

Study [ref]	Design	Setting/Data Source	Accrual period	Sample size	Inclusion criteria (Exclusion criteria)
Tuchsen et al., 2006 [221]	prospective cohort	Danish survey data	1990	5,517	20-59 yr, employed for at least one day within 2 months prior to the interview and responders to the question on work schedule
Vertin, 1978 [199]	prospective cohort	Viscose rayon factory workers	1968-1974	200	randomly selected workers at the factory (those taken off shift duty on medical reasons)
Virkunnen et al., 2006 [222]	prospective cohort	Helsinki Heart Study (clinical trial)	1987-1988	1,804	men, 40-55 yr, employed in industry, participants of Helsinki Heart study (missing information on occupation/shift work status, part-time work, night work, P/H of major illness)
Virtanen and Notkola, 2002 [205]	retrospective cohort	Finnish census data	1975-1980	385,500	25-64 in 1980 census, same occupation in 1975 and 1980 (mining work, military work and agricultural work)
Yadegarfar and McNamee, 2008 [161]	case-control	nuclear plant workers in Britain	1950-1998	1,270	all men, < 50 yr at accrual, worked at the plant for at least 20 days, blue collar workers (females, white collar workers)

Abbreviations: BMI body mass index, BP blood pressure, CVD cardiovascular disease, CHD coronary heart disease, HUNT Nord-Trøndelag health study, IHD ischemic heart disease, JACC Japan Collaborative Cohort for Evaluation of Cancer Risk, MI myocardial infarction, MONICA Northern Sweden Monitoring of Trends and Determinants of Cardiovascular Diseases, P/H past history, SHIP Study of Health in Pomerania, VIP Vasterbotten Intervention Programme, yr year

Table 4. Exposure characteristics

Study	Data source for exposures	Type of shift work	Definition
Akerstedt et al., 2004	interview	Mixed	working in three-shift work, night work, evening work, roster work and other forms
Alfredsson et al., 1985	ascertained at occupation level based on National Surveys	Irregular	irregular work was defined as any work other than day time work
Allesoe et al., 2011	self administered questionnaire	Rotating*, night and evening	differences in shift work types not reported
Babisch et al., 2005	interview	Unspecified	not defined
Biggi et al., 2008	municipality records	Night	working during 23:35 - 05:35 hours, Monday to Saturday number of years on the night work was also collected
Boggild et al., 1999	self administered questionnaire followed with an interview	Mixed	working irregular hours, shift work or often had night work
Brown et al., 2009	self administered questionnaire	Rotating	working at least 3 nights per month in addition to days or evenings in that month. number of years on such shifts was obtained and categorized as never, 1-2, 3-5, 6-9, 10-14 and ≥ 15 years
Ellingsen et al., 2007	company records	Rotating	working in rotating cycles starting with 2 morning, 2 afternoon followed by 2 night shifts
Falger and Schouten, 1992	interview	Unspecified	not defined
Fujino et al., 2006	self-administered questionnaire	Rotating* and night	*rotating*: working alternating day and night most of the time *night*: working night shifts most of the time

Study	Data source for exposures	Type of shift work	Definition
Fukuoka et al., 2005	interview	Night	working at night
Haupt et al., 2008	interview	Mixed	only former shift workers were included. number of years on shift work was recorded as 0, 1-5, 6-10, 11-20, > 20yr
Hermansson et al., 2007	self administered questionnaire	Mixed	working in shifts, at night, or variable hours
Hublin et al., 2010	self administered questionnaire (on two occasions, 1975 and 1981)	Unspecified* and night	working at night was defined as night work. 'shift work' was not explicitly defined
Karlsson et al., 2005	company files	Rotating	working in rotating shifts that change weekly: morning, evening and night number of years on shift was categorized as < 5 yr, ≥ 5 to < 10, ≥ 10 to < 20, ≥ 20 to < 30 and ≥ 30
Kawachi et al.,1995	self administered questionnaire	Rotating	working at least 3 nights per month in addition to days or evenings in that month. number of years on shift was categorized as never, 1-2, 3-5, 6-9, 10-14 and ≥ 15 years
Knutsson et al., 1986	interview	Rotating	working in rotating shifts for at least 6 months years on shift work was categorized as 0, 2-5, 6-10, 11-15, 16-20, > 20
Knutsson et al.,1999[§]	self administered questionnaire	Mixed* and night	*In past 5 years* *mixed*: working in shifts involving either evening or night shifts, with/without day shifts *night*: working at night, with/without evening shift or day shift
Koller, 1983	company files	Rotating	working in 3 shift rotating system years on shift work is categorized as 0-3, 4-12, 13-22 and 23-40 years

Study	Data source for exposures	Type of shift work	Definition
Laugsand, 2011	questionnaire	Mixed	working in shift work or night work shift work not defined
Liu and Tanaka, 2002	interview	Rotating	working in rotating shifts
McNamee et al., 1996	company records	Rotating	working for at least one month in a three shift, one week, forward rotating system. number of years on shift work was also obtained categorized as 0.1-1.9, 2-4.9, 5-9.9, ≥ 10 yr
Netterstrom et al., 1999	interview	Unspecified	not defined
Rafnsson and Gunnarsdottir, 1990	company records	Mixed	working in three shifts, day and night
Steenland and Fine, 1996	company records	Evening* and night	*evening*: working in 2nd shift *night*: working in 3rd shift
Tarumi, 1997	company records	Unspecified	not defined
Taylor and Pocock, 1972 (re-analyzed by Knutsson et al., 2004)	company records	Rotating	completed 10 years on shift work since 1946, any interruption being for less than six month
Taylor et al., 1972	company records	Mixed	working in either three-shift continuous, three-shift discontinuous, three-shift continuous (rapid rotating), permanent nights, alternate day and night, or double days
Tuchsen, 1993	ascertained at occupation level by Employment Classification Module (registry)	Unspecified*, evening, and night	individuals belonging to occupational groups, whose at least 20% of individuals report of evening work, night work or any other form of shift work
Tuchsen et al., 2006	interview	Mixed	working in either two, three, rotating, permanent evening, permanent night, permanent morning shifts or other non-day work
Vertin, 1978	company records	Unspecified	not defined

Study	Data source for exposures	Type of shift work	Definition
Virkunnen et al., 2006	questionnaire	Mixed	working in 2-shift work, 3-shift work, or irregular work
Virtanen and Notkola, 2002	ascertained at occupation level using Finnish job-exposure matrix	Evening* and night	not defined
Yadegarfar and McNamee, 2008	company records	Mixed	working in either of following shifts for a period of 30 days or more: three shift continuous with one week on one week off, seven-day double-day shifts, five-day double-day shifts. number of years on shift was categorized as 0.1-0.9, 1-4.9, 5-9.9, ≥ 10

* Shift schedule used for all analyses, except subgroup analysis by type of shift schedule

§ Night workers were a subgroup of the mixed type group

Table 5. Outcome characteristics

Study	Data source for outcomes	Outcome	Definition
Akerstedt et al., 2004	Swedish Cause-of-Death register	all cause mortality	total mortality regardless of cause (Chapter XVII [N800–959], according to the 8th and 9th revisions of the ICD
Alfredsson et al., 1985	Swedish hospitalization register	MI	hospitalization for acute MI (ICD 410.00, 410.99)
Allesoe et al., 2011	Danish National Patient Registry	coronary events	first ever hospitalization for IHD, including first ever MI, other acute or chronic IHD, angina or ECG-diagnosed heart disease (ICD-8 410-414, ICD-10 I20-25)
Babisch et al., 2005	hospital discharge records	MI	confirmed diagnosis of acute MI or survivors of sudden cardiac arrest (ICD-9 410) following the WHO definition including ischemic ECG changes, clinical symptoms and enzymatic changes
Biggi et al., 2008	periodic medical examinations by an occupational health physician	coronary events	incident diagnosis of coronary artery disease
Boggild et al., 1999	National Health Service register and Danish Institute of Clinical Epidemiology register	coronary events, all cause mortality	hospital admission for acute MI and death certificate diagnoses (ICD-8 410-414)
Brown et al., 2009	self-report, National Death Index, next-of-kin report, medical records, death certificates	ischemic stroke	evidence of a neurologic deficit with sudden or rapid onset that persisted for >24 hours or until death, confirmed by neuroimaging in 91% of those with medical records
Ellingsen et al., 2007	company medical records	coronary events	incident cases of coronary artery disease or MI

Study	Data source for outcomes	Outcome	Definition
Falger and Schouten, 1992	hospital records	MI	definite first acute MI based on clinical history, standard ECG readings and maximum plasma enzyme levels
Fujino et al., 2006	administrative data held at regional research centers	total and cause-specific mortality	cardiovascular death (ICD-10 I00-I99), coronary death (I20-I25), cerebrovascular death (I60-I69)
Fukuoka et al., 2005	hospital records	MI	elevated cardiac enzyme levels and a history of ischemic symptoms, relevant ECG changes or coronary artery intervention
Haupt et al., 2008	patient interview	MI	self-reported physician diagnosis of MI
Hermansson et al., 2007	reports from hospitals and general practitioners, hospital discharge registers and death certificates	ischemic stroke	WHO MONICA criteria
Hublin et al., 2010	administrative databases held at the Population Register Centre of Finland, Statistics Finland, the Finnish Social Insurance Institution and the Finnish Centre for Pensions	coronary death, cardiovascular events	for coronary death: underlying cause of ICD-10 I20-I24 and ICD-8/9 410-414 for cardiovascular events: disability retirement due to cardiovascular disease (ICD-10 I00-I99 and ICD-8/9 390-459)
Karlsson et al., 2005	National Cause of Death Register (Sweden)	total and cause-specific mortality	death certificate diagnosis in the primary or contributory cause-of-death fields, based on five consecutive revisions of the ICD (6th-10th)

Study	Data source for outcomes	Outcome	Definition
Kawachi et al., 1995	questionnaires, medical records, interview, patient letters, National Death Index, reports from next-of-kin and postal authorities	coronary events, MI, total, cardiovascular and coronary mortality	MI was defined according to WHO criteria; coronary death was defined as fatal MI or CHD recorded on the death certificate as the underlying and most probable cause with previous evidence of CHD (externally corroborated); coronary events was nonfatal MI or fatal CHD; cardiovascular mortality was death from CHD or cerebrovascular disease
Knutsson et al., 1986	death certificates, occupational health unit records, county hospital records, family members, autopsy reports	coronary events	WHO criteria for MI and/or angina defined by typical symptomatology (supported by positive ECG-exercise testing)
Knutsson et al., 1999	coronary and intensive care unit reports, hospital discharge registers and death certificates	MI	typical symptoms, blood marker changes, ECG changes and/or necropsy findings
Koller, 1983	history-taking on a prospective medical check-up	coronary and cardiovascular events	ischemic heart disease (ICD-9 414) and cardiovascular events (414, 440-448, 458, 401-405, 454-456) as classified by a panel of physicians
Laugsand et al., 2011	hospital records and death certificates	MI	European Society of Cardiology/American College of Cardiology consensus guidelines
Liu and Tanaka, 2002	admissions data for 22 hospitals	MI	ischemic cardiac pain lasting at least 30 minutes, enzyme change and supportive electrocardiography
McNamee et al., 1996	death certificates	coronary death	cause of death coded as IHD on the death certificate

Study	Data source for outcomes	Outcome	Definition
Netterstrom et al., 1999	coronary care unit admissions from two hospitals	MI	severe chest discomfort or ECG signs of MI accompanied by increased creatinine phosphokinase to at least twice the normal upper limit
Rafnsson and Gunnarsdottir, 1990	death certificates	coronary and total death	the officially classified underlying cause of death, reclassified according to ICD-7
Steenland and Fine, 1996	death certificates	coronary death	death due to IHD (ICD-9 410-414) while working or within 1 week of work, with no prior indication of heart disease in their records
Tarumi, 1997	death certificates	total and cardiovascular mortality	cardiovascular death listed on the death certificate and defined as death due to IHD (I20-I25) or stroke (I60-I69)
Taylor and Pocock, 1972a (re-analyzed by Knutsson et al., 2004)	death certificates	coronary, cerebrovascular, cardiovascular and total mortality	cause of death was coded in ICD-7 in accord with established rules for primary mortality tabulation
Taylor et al., 1972b	personnel records	cardiovascular events	medically certified absence from work lasting more than three days with a final diagnosis recorded as cardiovascular disease (excluding varicose veins and hemorrhoids)
Tuchsen, 1993	national inpatient register	coronary events	first admission with a discharge diagnosis of ICD-8 410-414
Tuchsen et al., 2006	national patient register containing all hospital discharge data, outpatient data and emergency room visits	cardiovascular and coronary events	first hospital contacts with a principal diagnosis of circulatory disease (ICD-8 390-458, ICD-10 I00-I99) or ischemic heart disease (coding unspecified)
Vertin, 1978	company medical records	coronary events	absenteeism statistics defined using ICD-7 (Dutch modification) codes for IHD

Study	Data source for outcomes	Outcome	Definition
Virkunnen et al., 2006	hospital discharge register and register of deaths	coronary events	ICD-8/9 410-414, ICD-10 I20-I25 (fatal or non-fatal)
Virtanen and Notkola, 2002	national death register (vital statistics)	cardiovascular, cerebrovascular deaths	cardiovascular (ICD-9 390-459) and cerebrovascular deaths (ICD-9 430-438)
Yadegarfar and McNamee, 2008	death certificates	coronary death	ICD 410-414 as determined from the code given by the UK Office of National Statistics

Abbreviations: ECG electrocardiogram, CHD coronary heart disease, ICD International Classification of Diseases, IHD ischemic heart disease, MONICA Monitoring of Trends and Determinants in Cardiovascular Diseases, WHO World Health Organization

Figure 4. Risk of bias in primary studies

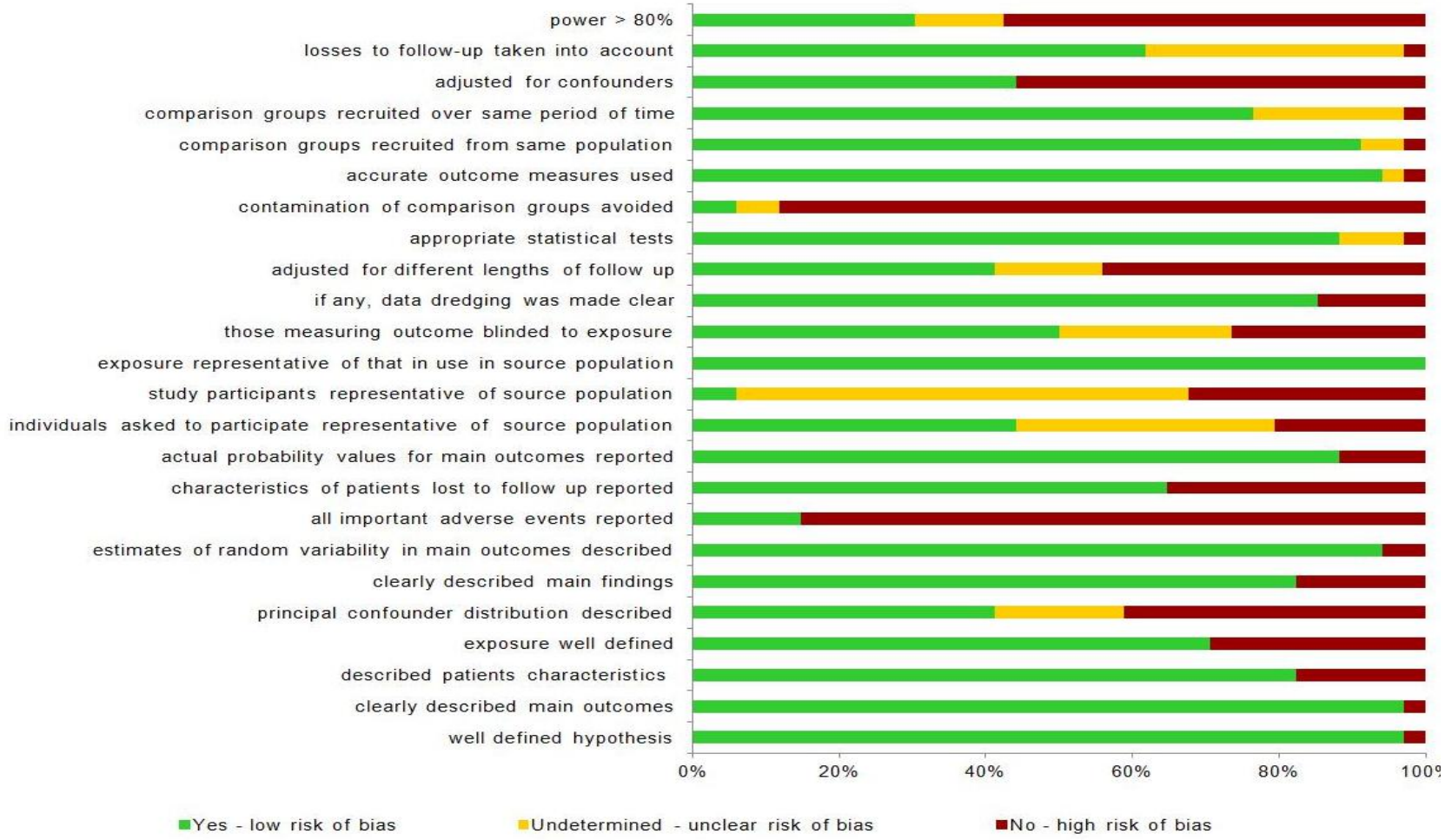


Table 6. Results of individual studies (restricted to shift schedule of primary interest)

Study	Outcome	Number of events	Risk estimate (95% CI)	Variables accounted for
Akerstedt et al., 2004	all cause mortality	864	HR 1.08 (0.90 – 1.31)	age, stress, physically strenuous work, smoking, chronic disease
Alfredsson et al., 1985[§]	MI	1201	SHR 1.20 (1.09 – 1.31)	age, county
Allesoe et al., 2011	coronary events	580	HR 0.81 (0.61 – 1.04)	age, family history, diabetes, menopause, BMI, smoking, alcohol consumption, leisure time activity, physical activity at work
Babisch et al., 2005[§]	MI	1881	OR 1.05 (0.89 – 1.25)	age, diabetes, hypertension, family history, smoking, BMI, employment status, living without a partner, noise sensitivity, education, sex*, hospital*
Biggi et al., 2008	coronary events	10	Risk Ratio 2.02 (0.43 – 9.40)	no covariate adjustment
Boggild et al., 1999	coronary events all cause mortality	1006 1659	RR 0.90 (0.70 – 1.10) RR 0.90 (0.80 – 1.10)	age, social class, sleep, tobacco, weight, height, fitness

Study	Outcome	Number of events	Risk estimate (95% CI)	Variables accounted for
Brown et al., 2009	ischemic stroke	1660	HR 1.05 (1.01 – 1.09)	age, questionnaire cycle, physical activity, BMI, alcohol, fruit, vegetable intake, menopausal status, smoking, hormone replacement, aspirin use, diabetes, coronary disease, blood pressure, serum cholesterol, husband's education, snoring, sleep duration, atrial fibrillation
Ellingsen et al., 2007	coronary events cardiovascular events	67 223	Risk Ratio 1.99 (1.23 – 3.22) Risk Ratio 1.89 (1.47 – 2.44)	no covariate adjustment
Falger and Schouten, 1992	MI	133	RR 1.59 (0.96 – 2.64)	age, exhaustion, smoking, education, hospital site*
Fujino et al., 2006	coronary death cerebrovascular death cardiovascular death all cause mortality	81 125 283 1282	RR 2.32 (1.37 – 3.95) RR 1.12 (0.66 – 1.91) RR 1.59 (1.16 – 2.18) RR 0.98 (0.82 – 1.17)	age, smoking, alcohol, education, perceived stress, past medical history, BMI, hours of walking, hours of exercise, job type
Fukuoka et al., 2005	MI	47	OR 1.57 (0.41 – 5.98)	age*, work status*, gender*
Haupt et al., 2008	MI	140	HR 1.53 (1.06 – 2.22)	age, sex, food frequency score, socioeconomic status, smoking

Study	Outcome	Number of events	Risk estimate (95% CI)	Variables accounted for
Hermansson et al., 2007[§]	ischemic stroke	194	OR 1.08 (0.69 – 1.70)	age, smoking, education, job strain, BP, serum triglycerides, cholesterol, sex*, survey*, survey date*, locale
Hublin et al., 2010[§]	coronary death	708	HR 1.11 (0.84 – 1.47)	age, marital status, social class, education, smoking, binge drinking, alcohol, hypertension, BMI, conditioning physical activity, life satisfaction, diurnal type, sleep length, use of hypnotics or tranquillizers, physical workload, working pace
	cardiovascular events	563	HR 0.72 (0.53 – 1.00)	
Karlsson et al., 2005	coronary death	662	RR 1.11 (0.95 – 1.30)	age, duration of employment
	cerebrovascular death	69	RR 1.56 (0.98 – 2.51)	
	all cause mortality	1850	RR 1.02 (0.93 – 1.11)	
Kawachi et al., 1995	coronary events	292	RR 1.31 (1.02 – 1.68)	age, smoking, diabetes, hypertension, hypercholesterolemia, past oral contraceptive use, current use of hormonal replacement, parental MI before age 60, alcohol, physical activity, BMI, aspirin use, quintiles of
	coronary death	44	RR 1.19 (0.63 – 2.23)	
	cardiovascular death	95	RR 1.46 (0.95 – 2.23)	
	MI	248	RR 1.34 (1.02 – 1.75)	

Study	Outcome	Number of events	Risk estimate (95% CI)	Variables accounted for
	all cause mortality	738	RR 1.29 (1.10 – 1.52)	vitamin E, follow-up period, husband's education
Knutsson et al., 1986	coronary events	43	OR 3.32 (1.33 – 8.26)	age, duration of exposure, smoking, family status
Knutsson et al., 1999[§]	MI	2006	OR 1.30 (1.10 – 1.53)	age*, sex*, residence*, smoking, job strain, education
Koller, 1993	coronary events cardiovascular events	7 45	Risk Ratio 5.17 (0.30 – 89.43) Risk Ratio 2.73 (1.12 – 6.64)	age*, duration of employment*
Laugsand et al., 2011	MI	606	HR 1.37 (1.14 – 1.66)	age, sex, marital status, education, shift work, systolic blood pressure, total cholesterol, diabetes mellitus, body mass index, physical activity, smoking, depression
Liu and Tanaka, 2002	MI	260	OR 1.12 (0.68 – 1.83)	age*, sex*, residence*
Mcnamee et al., 1999	coronary death	443	OR 0.85 (0.65 – 1.12)	age*, smoking, BMI, height, systolic BP, diastolic BP, job status, duration of employment, year of starting work*
Netterstrom et al., 1999	MI	76	OR 1.13 (0.54 – 2.39)	sex*
Rafnsson and Gunnarstdottir, 1990	coronary death all cause mortality	29 70	SMR 1.21 (0.72 – 1.91) SMR 1.01 (0.73 – 1.36)	age, calendar year

Study	Outcome	Number of events	Risk estimate (95% CI)	Variables accounted for
Steenland and Fine, 1996	coronary death	155	OR 1.01 (0.66 – 1.52)	age, worksite, race
Tarumi, 1997	cardiovascular death	72	OR 2.14 (0.63 – 7.31)	age, job site location, blue collar status*
	all cause mortality	171	OR 0.96 (0.59 – 1.56)	
Taylor and Pocock, 1972a (re-analyzed by Knutsson et al., 2004)	coronary death	409	SMR 1.03 (0.90 – 1.18)	age, calendar period, sex*
	cerebrovascular death	116	SMR 0.86 (0.64 – 1.11)	
	cardiovascular death	541	SMR 1.02 (0.90 – 1.14)	
	all cause mortality	1458	RR 1.03 (0.93 – 1.14)	
Taylor et al., 1972b	cardiovascular events	30	Risk Ratio 0.67 (0.32 – 1.37)	age*, organization*, occupation*
Tuchsen, 1993	coronary events	5407	SHR 1.74 (1.65 – 1.84)	age, sex*
Tuchsen et al., 2006	coronary events	130	RR 1.40 (0.90 – 2.12)	annoying noise, coldness, conflicts at work, high cognitive demands, ergonomic exposure, job insecurity, passive smoking, monotonous tasks, low decision authority, heat, walking or standing for long hours at work, low social support, BMI, current smoking
	cardiovascular events	562	RR 1.31 (1.06 – 1.63)	
Vertin, 1978	coronary events	4	Risk Ratio 1.00 (0.14 – 6.96)	carbon disulfide exposure*
Virkunen et al., 2006	coronary events	344	RR 1.30 (1.04 – 1.61)	age, smoking, systolic BP, cholesterol, BMI, gemfibrozil use, noise, physical workload

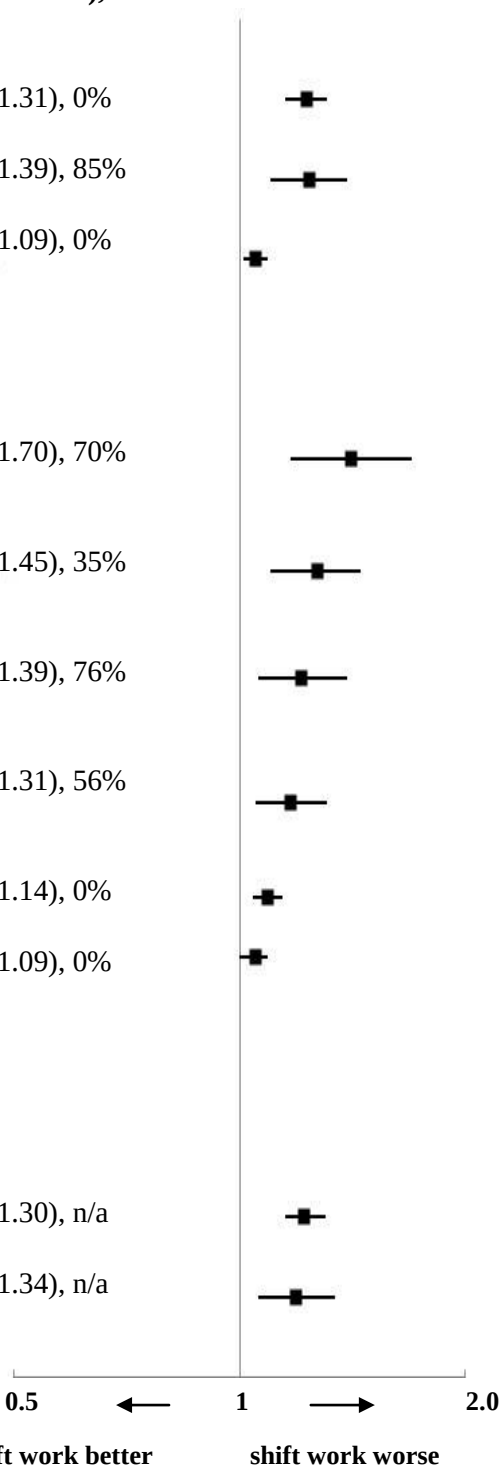
Study	Outcome	Number of events	Risk estimate (95% CI)	Variables accounted for
Virtanen and Notkola, 2002	cerebrovascular death	2428	Rate Ratio 1.19 (1.01 – 1.39)	age, marital status, professional status, education, income, socioeconomic status, job exposure variables
	cardiovascular death	16344	Rate Ratio 1.02 (0.96 – 1.08)	
Yadegarfar and McNamee, 2008	coronary death	635	OR 1.03 (0.83 – 1.28)	age*, year of starting work*, smoking, systolic BP, diastolic BP, BMI, height, work status, duration employment, social class

[§] risk estimates were pooled across stratifying variables using fixed effects model
* matching or stratifying variable

Abbreviations: BMI Body mass index, BP blood pressure, CI confidence interval, HR hazard ratio, MI myocardial infarction, OR odds ratio, RR relative risk, SMR standardized mortality ratio, SHR standardized hospitalization ratio

Figure 5. Pooled analyses for primary outcomes

Analysis	Events (studies)	Risk Ratio (95% CI), I^2
Myocardial infarction	6598 (10)	1.23 (1.15 to 1.31), 0%
All coronary events	17359 (28)	1.24 (1.10 to 1.39), 85%
Ischemic stroke	1854 (2)	1.05 (1.01 to 1.09), 0%
Sensitivity analysis[§]		
Myocardial infarction, unadjusted	4408 (5)	1.41 (1.17 to 1.70), 70%
Myocardial infarction, adjusted	4408 (5)	1.27 (1.10 to 1.45), 35%
Coronary events, unadjusted	8154 (12)	1.21 (1.06 to 1.39), 76%
Coronary events, adjusted	8154(12)	1.17 (1.05 to 1.31), 56%
Stroke, adjusted	1854 (2)	1.09 (1.04 to 1.14), 0%
Stroke, unadjusted	1854 (2)	1.05 (1.01 to 1.09), 0%
Trim and filled estimates[£]		
Myocardial infarction	12	1.22 (1.15 to 1.30), n/a
All coronary events	32	1.19 (1.06 to 1.34), n/a
Ischemic stroke[Φ]	-	-



[§] These analyses pooled the subset of studies which reported both unadjusted and adjusted risk estimates
[£] Includes hypothetical unpublished studies imputed according to the algorithm
[Φ] Duval and Twedie trim and fill method could not be applied, as only 2 studies were reported

Table 7. Pooled analyses for secondary outcomes using random effects model

Outcome	Events (studies)	Random effects risk ratio (95% CI)	I^2
Cardiovascular events	1423 (5)	1.24 (0.81 to 1.89)	85%
Coronary mortality	3166 (9)	1.08 (0.97 to 1.21)	29%
Cerebrovascular mortality	2738 (4)	1.12 (0.89 to 1.40)	52%
Cardiovascular mortality	17335 (5)	1.14 (0.98 to 1.32)	65%
All cause mortality	8092 (8)	1.04 (0.97 to 1.11)	36%

Figure 6. Funnel plot: effect of shift work on myocardial infarction

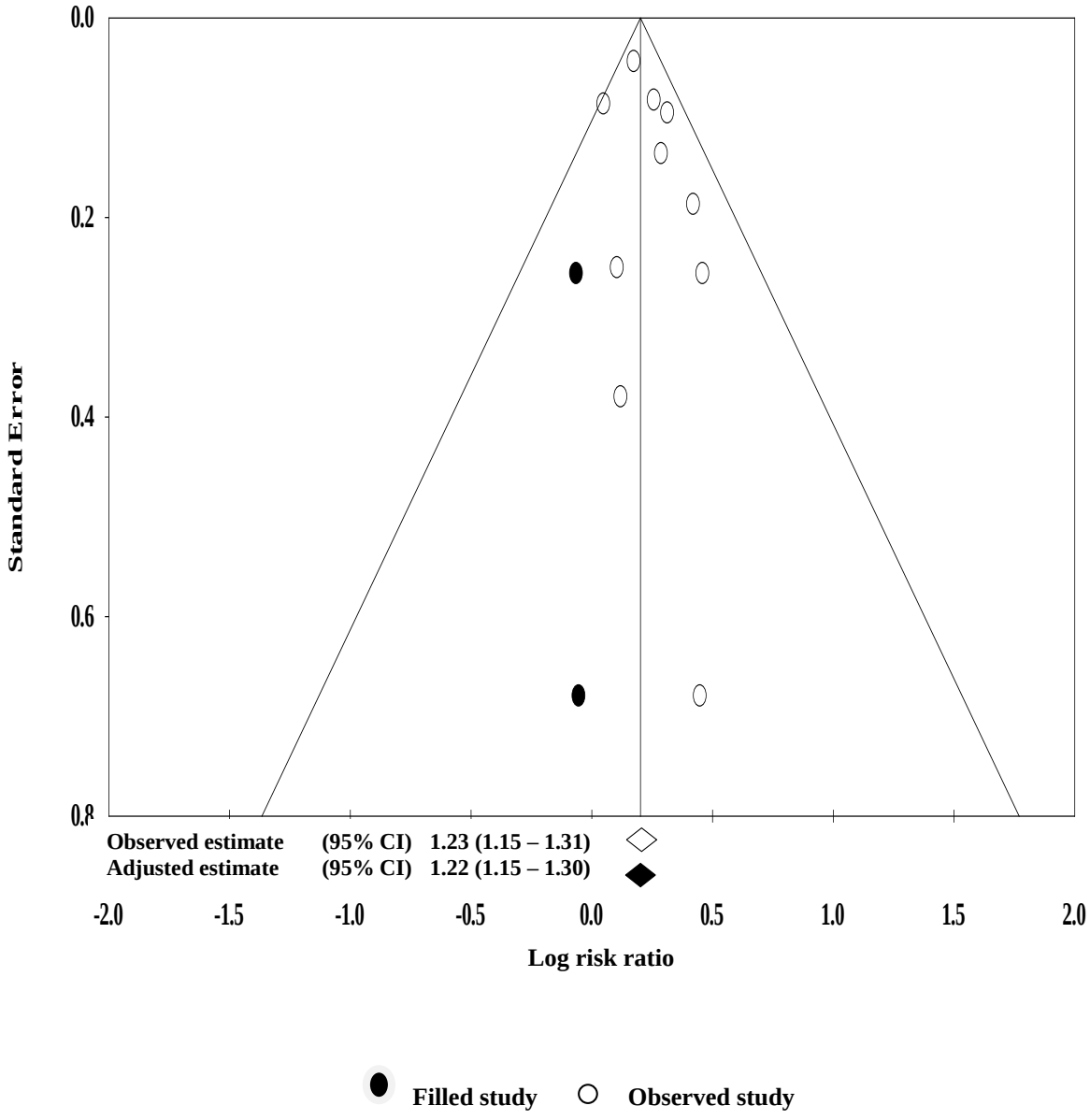


Figure 7. Funnel plot: effect of shift work on coronary events

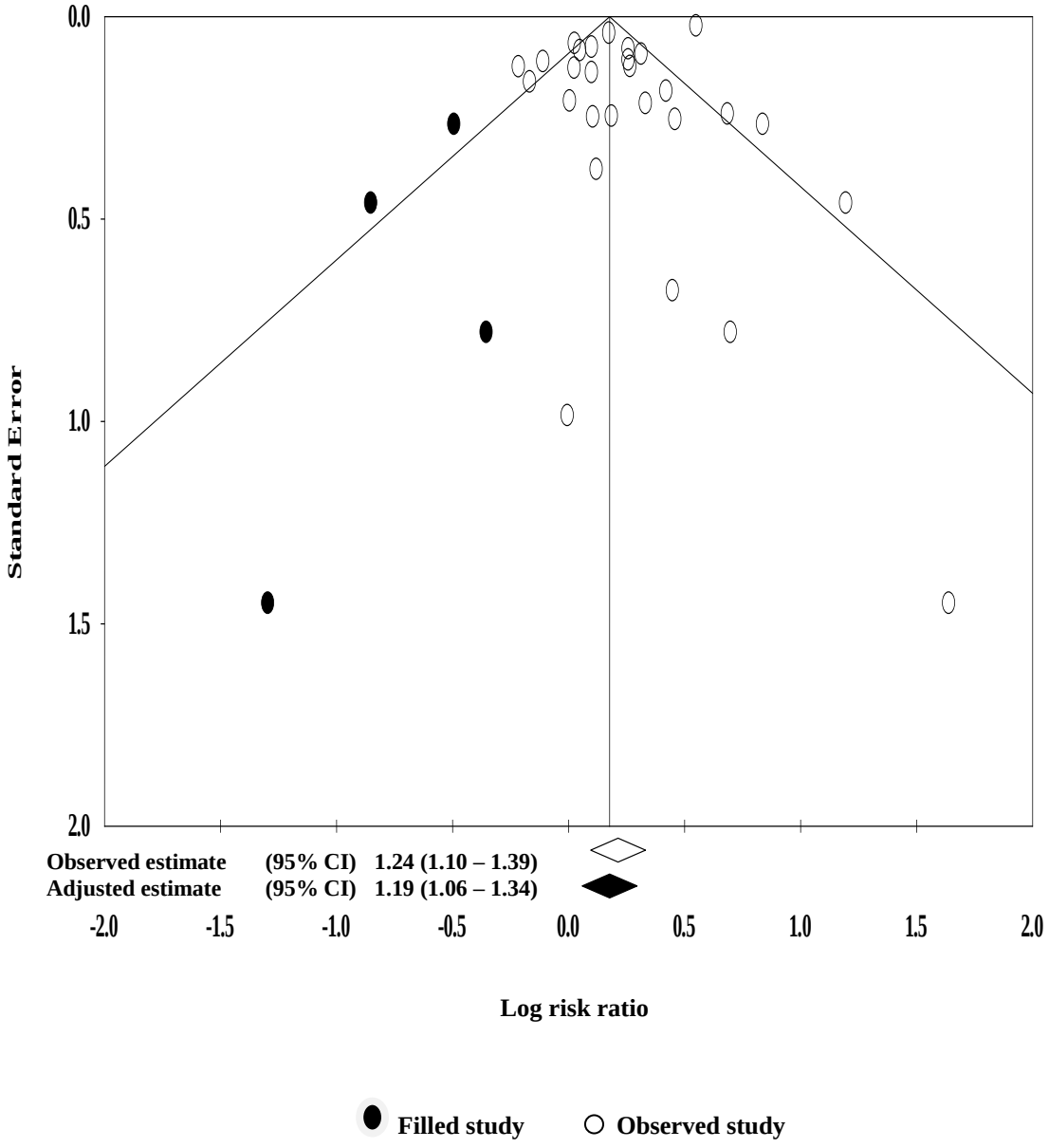
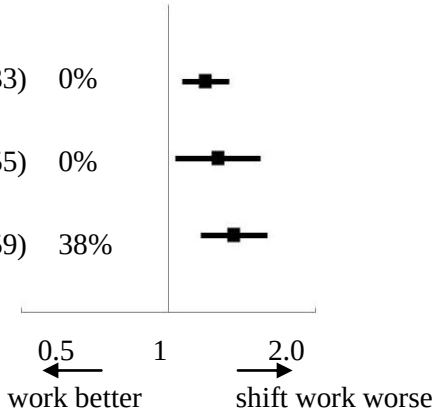


Table 8. Meta-regression results and subgroup analyses for coronary events

Covariate	Estimated β coefficient (95% CI)	*P* value	τ^2
study region (Europe vs. other)	0.17 (-0.09 to 0.44)	0.19	0.032
accrual start (per decade from 1940)	0.04 (-0.01 to 0.09)	0.11	0.029
maximum follow-up (per decade)	0.00 (-0.08 to 0.07)	0.95	0.044
sample size (per 1000 subjects)	0.00 (0.00 to 0.01)	0.44	0.018
% shift workers (of total sample)	-0.11 (-0.65 to 0.43)	0.70	0.031
mean age (per 10 years)	-0.01 (-0.12 to 0.11)	0.92	0.038
% female (of total sample)	-0.02 (-0.28 to 0.25)	0.90	0.035
% blue-collar (of total sample)	-0.02 (-0.28 to 0.24)	0.88	0.012
rotating shift work	-0.06 (-0.25 to 0.14)	0.57	0.031
event type (MI vs. other coronary event)	0.05 (-0.15 to 0.25)	0.63	0.033
data source for outcomes (primary vs. administrative data)	-0.17 (-0.37 to 0.02)	0.08	0.032
sample risk (events per 100-person-years)	-0.12 (-0.40 to 0.16)	0.39	0.420
control group (day workers vs. general population)	0.07 (-0.16 to 0.29)	0.54	0.032
adjustment (unadjusted vs. adjusted)	-0.50 (-1.06 to 0.06)	0.08	0.031
number of confounders adjusted for	-0.01 (-0.03 to 0.01)	0.28	0.032
SES-adjusted	-0.12 (-0.03 to 0.07)	0.21	0.031
smoking-adjusted	-0.12 (-0.31 to 0.07)	0.22	0.031
risk analysis incorporates follow-up time	0.06 (-0.14 to 0.27)	0.54	0.033
methodological quality (Downs and Black scale)	-0.60 (-1.46 to 0.26)	0.17	0.030
study power (1-β)	0.12 (-0.13 to 0.39)	0.34	0.029
duration of shift work (per decade)	0.01 (-0.12 to 0.13)	0.94	0.000
Subgroup analyses by shift schedule	**Risk ratio (95% CI)**	I^2	***P* value**
evening	1.29 (0.69 to 2.41)	94%	0.43
irregular or unspecified	1.28 (1.01 to 1.63)	92%	0.04
mixed	1.22 (1.08 to 1.38)	46%	0.001
night	1.41 (1.13 to 1.76)	36%	0.002
rotating	1.21 (1.00 to 1.46)	71%	0.0495

Figure 8. Subgroup analysis: risk of myocardial infarction in shift workers by different study designs

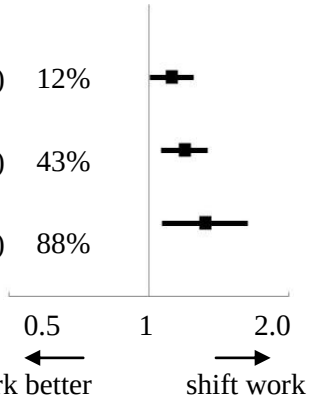
Subgroup	Number of studies	Risk ratio (95% CI)	I^2
case-control	6	1.19 (1.07 to 1.33)	0%
retrospective cohort	2	1.26 (1.03 to 1.55)	0%
prospective cohort	2	1.36 (1.17 to 1.59)	38%



Pooled risk ratio (95% CI) of myocardial infarction with shift work

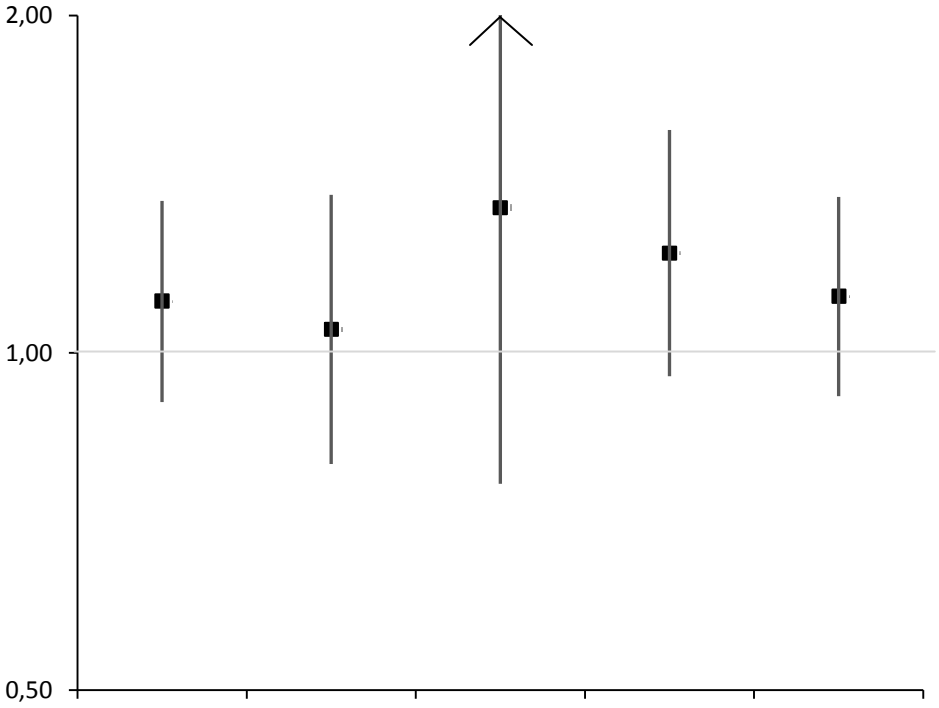
Figure 9. Subgroup analysis: risk of coronary events in shift workers by different study designs

Subgroup	Number of studies	Risk ratio (95% CI)	I^2
case-control	9	1.12 (1.00 to 1.15)	12%
retrospective cohort	8	1.19 (1.06 to 1.34)	43%
prospective cohort	11	1.32 (1.07 to 1.63)	88%



Pooled risk ratio (95% CI) of coronary events with shift work

Figure 10. Dose-response relation of shift work with coronary events



	very low (n = 5)	low (n = 6)	medium (n = 3)	high (n = 6)	very high (n = 6)
risk ratio (95% CI)	1.12 (0.90-1.37)	1.05 (0.80-1.38)	1.35 (0.76-2.38)	1.23 (0.95-1.58)	1.12 (0.91-1.38)
Average shift work duration	**1 y**	**5y**	**11y**	**12 y**	**16y**

categories of shift work exposure
(n is the number of studies in each category)

Figure 11. Risk of coronary events in ex-shift workers

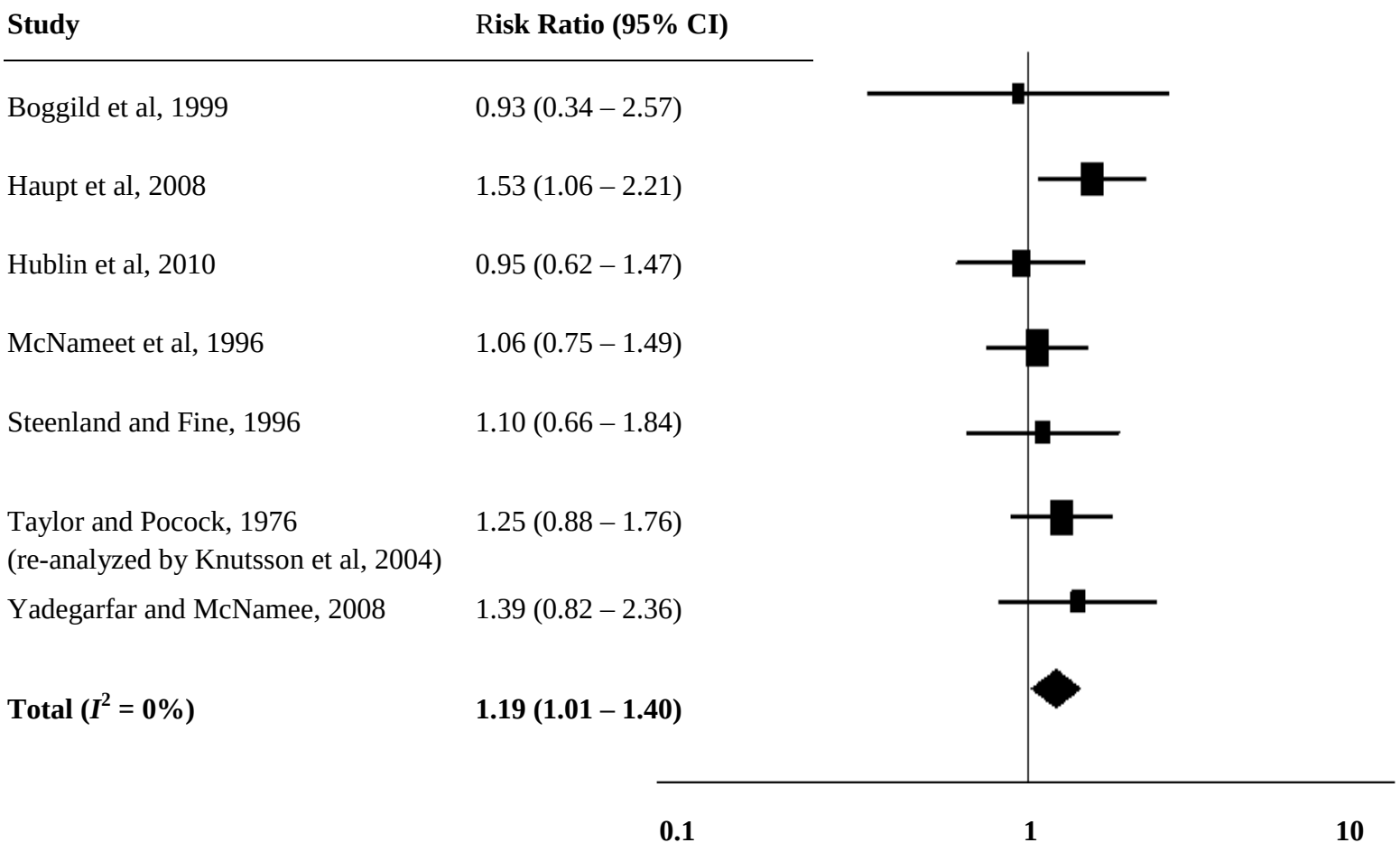


Table 9. Summary of findings

Question: Does shift work increase the risk of cardiovascular events?

Population: individuals currently employed or ever employed

Exposure: shift work defined as any work schedule other than day work

Comparison: day workers or the general employed population[1]

Perspective: shift workers in developed countries

Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Number of participants (studies)	Relative effect (95% CI)	Quality of evidence (GRADE)
Myocardial infarction	not likely[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	not likely[6]	1082977 (10)	1.23 (1.15 to 1.31)	moderate[2,3,4,5,6,7] ⨁⨁⨁◯
Coronary events	not likely[2]	inconsistency[8]	no serious indirectness[4]	no serious imprecision[5]	not likely[6]	1530070 (28)	1.24 (1.10 to 1.39)	low[2,4,5,6,7,8] ⨁⨁◯◯
Ischemic stroke	not likely[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	undetected[9]	80787 (2)	1.05 (1.01 to 1.09)	moderate[2,3,4,5,7,9] ⨁⨁⨁◯

[1] shift work event rates were compared with population event rates for three studies
[2] median Downs and Black score for the included studies was 60% (interquartile range, 18%)
[3] (I^2 = 0%)
[4] population, outcome and intervention were consistent with the question of interest although individuals studies varied
[5] number of events and number of participants studied in the review is large and the confidence interval does not include the null value
[6] publication bias-adjusted estimates did not differ from the observed estimates
[7] dilution effect of single time-point exposure ascertainment allows upgrading of evidence
[8] (I^2 = 85%)
[9] publication bias could not be tested for n = 2 stroke studies

Abbreviations: CI confidence interval, GRADE The Grading of Recommendations Assessment, Development and Evaluation

Chapter 4 Discussion and conclusion

1 Summary of evidence

To our knowledge, this is the first comprehensive review of the literature that quantifies the effect of shift work on clinically relevant cardiovascular outcomes. We mounted a large systematic search of more than 12,000 citations and screened these using a uniform set of prespecified criteria. We found moderate quality evidence of an increased risk of myocardial infarction (increased by 21%) and ischemic stroke (increased by 5%) in shift workers according to the GRADE approach, considering the risk of bias, inconsistency, imprecision, indirectness and publication bias.[174] We conclude that the true effect will be close to the reported estimate of the effect, but there is a possibility that it can be substantially different.

The evidence on the shift work-coronary event association (increased by 24%) is low quality because of substantial heterogeneity; therefore, our confidence in the estimated effect is limited. We conducted various meta-regression analyses to identify heterogeneity in the observed effects based on patient and study characteristics, but these analyses failed to explain the observed heterogeneity. However, the ability of meta-regression to examine the effect of covariates using study-level averages of patient characteristics is limited due to ecological bias.[223] We did not find marked differences between the association of shift work and coronary events by the type of shift schedule, level of adjustment or presence of publication bias. The association between evening shift work and coronary events was statistically non-significant, but the effect estimates were again heterogeneous across studies.

We found that the risk of all cardiovascular events increased in shift workers, but was statistically non-significant, which could be due to epidemiologically imprecise definitions of cardiovascular events, encompassing a wide range of circulatory diseases. The higher risks of coronary mortality, cerebrovascular mortality and cardiovascular mortality among shift workers were statistically non-significant and heterogeneous. Therefore, higher risk of non-fatal disease events does not seem to translate into higher cause-specific mortality in shift workers. The 'selection out' of shift workers with elevated cardiovascular risk could be one explanation. Individuals at an elevated cardiovascular risk may leave shift work to prevent disease, or following non-fatal

disability. The results from the subgroup analyses studying the risk of all coronary events in ex-shift workers supported such a dilution effect as the risk of coronary events decreased in ex-shift workers, although the decrease in the risk estimate effect was small. Conversely, the association between the prevalence of cardiovascular disease or cardiovascular risk factors (i.e. hypertension, diabetes, high cholesterol) and quitting shift work to perform day work was non-significant in one study that followed 7,037 female nurses.[63] The duration of follow-up was only 2 years. Moreover, only a few participants quit shift work to perform day work (n = 260); hence there was limited power to detect a significant association.[63] Occupational health screening at workplaces may be another factor leading to 'selection out' of high-risk shift workers reducing the cause-specific mortality in shift workers. It is also important to note that over the last four decades there have been great improvements in the management of cardiovascular disease in developed countries, decreasing the cause-specific mortality rates of myocardial infarction, acute coronary syndromes and ischemic stroke.[224, 225] This may also be a reason for the non-significant results of cause-specific mortality in shift workers.

The results from this meta-analysis concur with previous reviews that reported 1.4 times higher risk of ischemic heart disease in shift workers.[12, 101, 132] Shift work may contribute to cardiovascular disease through a variety of mechanisms. First, shift work is associated with circadian disruption[226], which could influence cardiovascular risk. While the central circadian rhythm is an important factor for maintaining cardiovascular function[227], recent studies have suggested an intrinsic tissue level circadian rhythm plays an important role too.[228] Various studies using animal models have found an increased risk of cardiovascular disease with circadian disruption.[131, 229, 230] Second, shift work leads to work-life imbalance and psychosocial stress, which are associated with an increased risk of cardiovascular disease.[67] Third, shift work leads to decreased sleep quantity and quality.[23] A recent meta-analysis found a statistically higher risk of coronary heart disease (pooled risk ratio 1.48, 95% confidence interval 1.22 to 1.80) and stroke (pooled risk ratio 1.15. 95% confidence interval 1.00 to 1.31) with short sleep duration.[231] Abnormal alterations in surrogate markers for cardiovascular disease have been found in short-term shift workers using an experimental study design.[113]

2 Strengths

This study was conducted in accord with published standards for executing and reporting meta-analyses of observational studies.[146] In comparison to previous systematic reviews[12, 101, 132], our work employed a comprehensive search strategy, searching for relevant articles in six different databases and various sources of grey literature. We prespecified broad inclusion criteria in order to encompass different studies. Reviewers performed the article screening, independently and in duplicate to reduce potential biases. We did not find a significant role of publication bias, assessed by Duval and Tweedie's trim-and-fill method, in the observed risk estimates for primary outcomes.

The Cochrane Collaboration and the PRISMA guideline authors urge systematic reviewers to assess methodological quality of included studies.[141, 142] In comparison to past reviews that did not perform this appraisal[132] or used invalidated assessment tools[12, 101], we used the Downs and Black checklist to critically appraise the study quality, which to our knowledge is the only validated checklist for methodological quality of observational studies.[158] The methodological quality of included studies in the review was at least moderate. Moreover, the pooled risk ratios for myocardial infarction and coronary events in the subgroup of prospective cohort studies, which are considered methodologically stronger, were higher when compared to that in retrospective cohort studies or case-control studies. This further strengthens our confidence in the results.

A major problem with meta-analyses is the lack of consistent definition of outcomes across different studies. The definitions of outcomes in this review were consistent across different studies and most studies (n = 32) used validated methods for outcome reporting suggesting consistency in outcome reporting.

A caveat that is specific to observational studies is poor control over potential confounding. The risk ratios obtained from the sensitivity analyses by separately pooling adjusted and unadjusted risk ratios in a subset of studies that reported both types of estimates differed only slightly, suggesting a minimal effect of confounding. We also found that associations did not differ statistically between studies that did not adjust for important confounders (socioeconomic class or smoking) when compared to those that

adjusted for these confounders; nor was the total number of confounders adjusted for important. Despite the robustness of these risk estimates, the effect of residual confounding cannot be ruled out.

3 Limitations

3.1 Validity of included studies

Selection bias is a major concern in observational studies. Selection bias occurs in shift work research at more than one level and unfortunately leads to bias in both directions.[182] Because our review is limited by the evidence that is available, we were not able to test the effects of all biases. The 'healthy worker bias' is a common type of selection bias in occupational medicine. It occurs when disease event rates in the employed individuals are compared to those in the general population.[232] Such bias leads to underestimation of the effect of exposure on outcome because employed individuals are considered healthier than the general population.[232] The statistically non-significant results of meta-regression to study the effect of type of comparison group (i.e. day workers vs. general population) on the shift work-coronary event association suggests that the results were unlikely to be affected by 'healthy worker bias'.

Another methodological flaw that is responsible for various exposure ascertainment biases is the dynamic nature of shift work exposure. Unfortunately, only a few studies in the review assessed shift work exposure longitudinally.

Comparatively few studies included in the meta-analysis excluded participants with a history of cardiovascular disease at baseline. The risk of recurrence in individuals with a history of cardiovascular disease is high.[233] Such individuals are less likely to work in shifts after a cardiovascular event; they therefore tend to assort to the control group.[234] Including individuals with a history of cardiovascular disease in studies underestimates the effect of shift work because the baseline risks in the exposed and the non-exposed groups are consequently not comparable.

3.2 Applicability

Our meta-analysis was limited to English-language publications. Although literature on shift work-cardiovascular disease associations was primarily published in the English language, the possibility of reports in other languages cannot be excluded, as our filters would have "automatically" weeded out such reports.

Second, the results of our study should be generalized to women with caution because the studies included in the review predominantly studied male populations. Yet our meta-regression analysis suggested that the proportion of females in each study did not alter the association between shift work and coronary events. For ischemic stroke, moreover, one study included data from female nurses only while the other included data from both male and female participants.[133, 212]

Third, the applicability of our results to shift workers in developing countries is not known. The evidence obtained in this review is mainly from developed countries with more rigorous health care systems and stricter legislation for working hours and worker health than developing countries. The prevalence of shift work is rising in developing countries due to rapid globalization and economic growth. Concurrently, the burden of cardiovascular disease in these countries is also increasing.[2] Therefore, future studies should quantify the shift work-cardiovascular disease association in workers of these countries.

We observed a non-linear dose-response relation between shift work and coronary events. This dose-response relation could be distorted due to the heterogeneous cut-points used to determine different categories of duration of shift work in different studies. Despite this heterogeneity, we found that the association between duration of shift work and incidence of coronary events followed an inverted U shaped curve. This concurs with previous studies that reported a similar relation.[161, 215] The healthy worker survivor bias is a possible explanation for the observed inverted U shaped relation. The most likely reason is that workers who have survived to enter the top quintile of shift work exposure are likely inherently healthier than those who have died or dropped out earlier. In addition, workers who work in a particular work schedule for an extensive period are likely to

adapt to their work schedule. As a result, the psychosocial stress wears off in such workers reducing their risk of developing disease. This could possibly explain the inverted U shaped relationship between shift work and coronary events. Moreover, competing risks in workers increase over time as they get older thus diminishing the strength of shift work and coronary disease association.

Finally, causal inferences from observational studies are not always well accepted. The results of this review are based on observational studies. Therefore, it is not possible to conclude that shift work is causally related to cardiovascular disease. We assessed the overall quality of evidence based on the GRADE approach, which is built on the principles of the Bradford Hill criteria of causality; hence, we believe that the association of shift work with our primary study outcomes (myocardial infarction, coronary events and ischemic stroke) merits serious consideration.[235]

4 Public health impact

We report higher risks of cardiovascular disease in shift workers. Although the increase is modest in comparison with the classical cardiovascular risk factors, the prevalence of shift work exposure in the adult population is much higher than that of most cardiovascular risk factors. We calculated the prevalence of shift work in the working population, aged over 15 years, who had ever been employed in the past 12 months prior to the General Social Survey, 2010 conducted by Statistics Canada. We downloaded the public use file of the General Social Survey 2010 [Canada]: Cycle 24: version 4 edition to undertake this analysis. We found that 32.8% of Canadians, who were ever employed between the years 2009 and 2010, worked in shifts other than day shift. The population-attributable risks of primary outcomes due to shift work were calculated by the following standard formula[236, 237]:

$$PAR = \frac{P_e(RR - 1)}{1 + P_e(RR - 1)}$$

P_e = prevalence of shift work among working Canadians (0.328)
RR = pooled risk ratio of developing outcome of interest in shift workers

The population-attributable risk is used to quantify the fraction of the population's incidence of a given disease that can be accounted for by the presence of a particular risk

factor. Thus, a higher fraction merits directing resources towards managing the risk factor.[238]

We found that the population-attributable risk from shift work was 7.0% for myocardial infarction and 7.3% for all coronary events. The population-attributable risk from shift work for ischemic stroke was 1.6%. Despite the relatively modest magnitude of association between shift work and the primary outcomes of interest, we found relatively substantial population-attributable risks for these outcomes from shift work. Therefore, public health measures are necessary to improve the health of workers.

5 Measures to reduce the risk

Various measures have been proposed to reduce cardiovascular risk in shift workers. These measures help shift workers to adapt to their work schedules by targeting various pathways involved. Overall, these measures can be divided into four major categories.

5.1 Lifestyle measures

Non-pharmacological measures for improving sleep quality and quantity in shift workers include planned napping during night shifts and timely light exposure.[239] Other measures such as healthy eating and avoiding heavy meals past midnight, improving physical fitness, having routine sleep patterns and developing active coping strategies have been shown to improve the quality of sleep in shift workers, helping them to adapt to shift work.[240] Social support at home and at workplace may be particularly important to reduce the risk of cardiovascular consequences of shift work. Social support may directly mitigate the psychosocial problems associated with shift work. It must be noted, however, that long-term effects of the above measures on cardiovascular outcomes have not been studied.

5.2 Therapeutic management

Melatonin has been proposed for therapeutic management of circadian disruption. This is a compound produced by the pineal gland that can induce time-dependent phase shifts in the circadian clock to correct the mismatch in the circadian rhythm[241, 242] The chronobiotic effects of melatonin may improve sleep quality and quantity in shift workers

and decrease fatigue, both of which can help shift workers adapt to their shift schedules.[243] While the safety of short-term exogenous melatonin administration has been shown in a meta-analysis[244], the safety of long-term exposure is not known. Moreover, whether the use of melatonin reduces cardiovascular risk is unknown.

5.3 Ergonomically designed shift systems

From the results of our subgroup analyses, we could not find a specific type of shift schedule that is beneficial for shift workers. The incidence of chronic conditions in male rotating shift work was reported to be statistically increased in a Canadian study (odd ratio 1.7; *P* value < 0.05), concurring with the results from our analyses.[19] Multiple failed attempts have been made to develop specific shift schedules that are less harmful. The forward rotating shift systems were reported to be physiologically less stressful than other shift systems in a systematic review by Driscoll et al.[245] However, to date backward rotating shifts have not been shown to be more detrimental than forward rotating shifts.[246]

In general, the recommendations for designing an ergonomically acceptable shift schedule include: a) avoiding night shift work whenever possible, or at least reducing the number of consecutive night work, b) selection of forward rotating over backward rotating shifts, c) avoiding work on weekends, and d) avoiding interposing a single workday between days off.[247] The quality of sleep and self-reported health was accessed in a group of 118 shift workers 15 months after changing their shifts to ergonomically well-designed shifts. The authors found that both sleeping patterns and self-perceived health improved after implementing the new system. However, this study was a pre-post analysis and therefore is subject to Hawthorne effect.[248] Another study reported better health and satisfaction rates in shift workers after introduction of a well-designed shift system.[249] It should be noted, however, that a system developed for one workplace may not always work well with other workplaces; yet by applying general principles of shift scheduling, healthier working pattern for shift workers might be achieved.

5.4 Health promotion and surveillance

The first three measures improve the adaptability of workers to shift systems and the

short-term advantages of these measures have been studied; however, their role in reducing cardiovascular disease morbidity or mortality has not been studied. Moreover, none of these measures can completely eliminate circadian rhythm disruption associated with shift work.

Strategically, applying population-based health programs to a group at higher risk for disease is considered more effective in the reducing incidence of disease than screening the entire population to identify all those at higher risk of the disease.[250] Shift-workers in a workplace represent a unique homogeneous group of individuals performing similar work under similar conditions. Education is an important factor for changing the health behaviours. Awareness programs for shift workers before starting shift work may be important for improving the health of shift workers. Other health promotion programmes specifically targeted to shift workers can also be effective.[251] The effect of one such program, which included (i) routine medical examination including an assessment of suitability for shift work, (ii) health promotion retreats lasting up to three weeks and (iii) financial compensation for employees leaving shift work for health problems, was tested in a study that followed 31,346 male workers in Germany for a period of 11 years.[252] In comparison to day workers, who were not offered this program, shift workers had marginally lower risks for overall mortality, taking age and job level into consideration. The risk ratio of ischemic heart disease in shift workers when compared to day workers was 0.74 (95% confidence interval 0.57 to 0.96) suggesting that the program reduced the cardiovascular risk in shift workers.[252] The risk of cerebrovascular disease, however, was not significantly altered.

In summary, different measures exist to help individual shift workers to adapt to their shift schedules and health promotion programmes for shift workers may reduce cardiovascular risk to a certain degree.

6 Possibilities for future research

Ideally, future epidemiologic studies should consider assessing shift work exposure longitudinally in order to record the movement of workers in and out of shift work. Such a method of exposure ascertainment will be able to delineate some of the selection biases

that exist when studying shift workers.

Also important is proper ascertainment of a fuller array of potential confounders and their adjustment. The sensitivity analyses suggested only a marginal effect of confounders; however, residual confounding should be considered. Mediators such as cardiovascular risk factors and certain lifestyle factors should ideally not be co-adjusted when the studying the association of shift work and cardiovascular disease, but if adjusted, both crude and fully adjusted estimates should be reported for ease of interpretation.

7 Conclusions

It is important for general practitioners and occupational health professionals to recognize shift work as a potential risk factor for cardiovascular disease. Therefore, we recommend that a history of shift work exposure should be explored in workers with elevated cardiovascular risk. Unfortunately, the present literature is scant on interventions that can eliminate the higher risk in shift workers. Perhaps the only way to do this is to avoid exposure to shift work. However, as mentioned previously, shift work is inevitable in certain occupations. Therefore, we speculate that early detection of short-term and long-term health effects among shift workers might help avoid the serious consequences of shift work.

Public health officials and policy makers should consider developing health programmes, either at the workplace or at a population level to protect, promote and restore the health of shift workers.

Appendices

Appendix A. Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist

Checklist	Page number
Reporting of background should include	
Problem definition	2 & 25
Hypothesis statement	28
Description of study outcome(s)	22
Type of exposure or intervention used	3
Type of study designs used	31
Study population	25
Reporting of search strategy should include	
Qualifications of searchers (e.g. librarians and investigators)	32
Search strategy, including time period included in the synthesis and keywords	32
Effort to include all available studies, including contact with authors	34
Databases and registries searched	32
Search software used, name and version, including special features used (e.g., explosion)	105
Use of hand searching (e.g. reference lists of obtained articles)	32
List of citations located and those excluded, including justification	54
Method of addressing articles published in languages other than English	32
Method of handling abstracts and unpublished studies	49
Description of any contact with authors	45
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	31
Rationale for the selection and coding of data (e.g. sound clinical principles or convenience)	34
Documentation of how data were classified and coded (e.g. multiple raters, blinding, and interrater reliability)	34

Checklist	Page number
Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate)	35
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	35
Assessment of heterogeneity	37
Description of statistical methods (e.g. complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	37, 49
Provision of appropriate tables and graphics	35, 37
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	120
Table giving descriptive information for each study included	55, 61 & 65
Results of sensitivity testing (e.g. subgroup analysis)	49
Indication of statistical uncertainty of findings	49
Reporting of discussion should include	
Quantitative assessment of bias (e.g. publication bias)	90
Justification for exclusion (e.g. exclusion of non–English-language citations)	92
Assessment of quality of included studies	90
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	88
Generalization of the conclusions (i.e. appropriate for the data presented and within the domain of the literature review)	92
Guidelines for future research	96
Disclosure of funding source	-

Appendix B. Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) guidelines

Section/topic	Item No	Checklist item	Page number
Title	1	Identify the report as a systematic review, meta-analysis, or both	ii
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	iii
Rationale	3	Describe the rationale for the review in the context of what is already known	25
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	28
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	-
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	31
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	32
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	32
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	34

Section/topic	Item No	Checklist item	Page number
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	34
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	34
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	35
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	37
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	37
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	38
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	38
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	54
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	46
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	48

Section/topic	Item No	Checklist item	Page number
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	48
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	77
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	49
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	50
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	52
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	91
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	96
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	-

Appendix C. Study eligibility criteria

Shift work and cardiovascular outcomes - Study Adjudication

Ref Man # **Reviewer initials:**
Primary Author's last name: **Year of publication:**

All criteria must be met

I Study comparison: shift work vs. controls	**YES**	**NO**
▪ Study included a defined group of subject that performed shift work	☐	☐
▪ Alternatively, comparisons can include: "night shift" vs. "day shift", "rotating vs. non-rotating/fixed shift", "irregular vs. regular shift", "evening vs. day shift" or "high intensity vs. low intensity shift"	☐	☐

II Outcomes	**YES**	**NO**
▪ Study measured at least one type of cardiovascular event* **<u>or</u>** death (*myocardial infarction, cardiovascular death, any coronary event, cardiac arrest, heart failure, stroke, sudden death)	☐	☐
▪ Study included information to calculate n/N for events in at least two groups (shift and control), where n is the # of patients incurring event and N is the # of patients in each group. If n/N is not provided, the study should have information from which n/N can be derived e. g. incidence rates/cumulative incidence, K-M curves, etc. **<u>OR</u>** Risk estimates (odds ratio, risk ratio, hazard ratio or relative risk) along with 95% confidence interval (or SE or p value) for association of shift work with events should be available	☐	☐

III Exclusion criteria	**YES**	**NO**
▪ Outcome is subjective cardiovascular complaint or symptom without physician-attributed diagnosis or objective verification	☐	☐

IV Final Reviewer's Assessment	**IN**	**OUT**
	☐	☐

Manuscript reporting	**IN**	**OUT**

Reliability statistics: Final decision – What was the final decision on the paper? ☐ ☐

Additional Notes:

Appendix D. Search strategies

Database	Search strategy
Medline	1. exp Cardiovascular Diseases/ or exp Cerebrovascular Disorders/ or exp Cardiovascular Agents/ or exp Cardiovascular System/ or Actuarial Analysis/ or Cause of Death/ or Death Certificates/ or Death, Sudden/ or Death/ or exp Morbidity/ or Fatal Outcome/ or Hospital Mortality/ or Life Expectancy/ or Life Tables/ or Mortality/ or Vital Statistics/ 2. Blood Pressure Monitors/ or Blood Pressure/ or exp Blood Pressure Determination/ or Hypertension/ or (blood pressure$ or hypertens$ or BP or SBP or DBP or diastolic$ or systolic$ or antihypertens$ or prehypertens$). mp. 3. (((hazard$ or cox) adj2 model$) or ((systolic$ or diastolic$) adj2 (dysfunction$ or function$)) or (arterial adj2 (occlusive or obstructive)) or (diabet$ adj2 (angiopat$ or microangiopat$)) or (ventric$ adj2 (dysfunction$ or function$ or rhythm$ or tachycardia$)) or actuarial$ or aortocoronar$ or angina or arrhythmi$ or arteriosclero$ or asystole$ or cad or cardi$ or carotid$ or cerebral$ or cerebro$ or chd or chf or coronary$ or cva$1 or or dead or death$ or died or dying or embol$ or fatalit$ or heart or ihd or infarct$ or isch?emi$ or kaplan meier$ or kaplan-meier$ or lethal$ or life table$ or lifetable$ or mi or morbid$ or mortalit$ or myocardi$ or stroke$1 or thrombol$ or thrombos$ or vascular$ or vasculatur$). mp. 4. or/1-3 5. ((on-call or oncall) and (duty or duties or hours or shift$1)). tw. 6. ((shift$1 or post-shift$ or postshift$ or one-shift$ or two-shift$ or three-shift$) adj5 (duty or duties)). tw. 7. ((shift$1 adj (system$1 or breaks or hour$)) or (hour$ adj shift$1)). tw. 8. (shiftwork$ or shift-work$ or night-shift$ or nightshift$ or night work$ or nightwork$ or night-work$ or off-shift$ or night-call$1). tw. 9. ((overnight or night$ or float$) adj5 (schedul$ or call or on-call or oncall)). tw. 10. ((alternating or work$ or schedule$ or rotating or backward-rotat$ or extended$ or forward-rotat$ or night$ or day-night$ or overnight$ or unconventional or roster$) adj3 (shift$1 or post-shift$ or postshift$ or one-shift$ or two-shift$ or three-shift$)). tw. 11. ((night$ adj2 (duty or duties or float$ or work$)) or (atypical adj (schedule$1 or shift$1 or hour$1)) or (hour$1 adj2 (float$ or work$))). tw. 12. ((roster$ or work or alternating or rotating or night$) adj1 schedul$). tw. 13. Night Care/ma or exp Work Schedule Tolerance/ 14. or/5-13 15. (ergonomics or occupational or industrial). jw. not ((microbiology or physiology or hygiene). jw. or Occupational Exposure/ or expos$. ti. or (torque$ or cycling$). tw.) 16. Personnel Staffing and Scheduling/ or Chemical Industry/ or exp

	Medical Staff/ or exp Nursing Staff/ or exp Work/ or Food Industry/ or Industry/ or Metallurgy/ or Occupational Diseases/ or Occupational Groups/ or Occupational Health/ or Occupational Medicine/ or Occupations/ or Railroads/ or Textile Industry/ or Workload/ or Workplace/ or ma. fs. 17. or/15-16 18. Chronobiology Disorders/ or Circadian Rhythm/ or "Sleep Disorders, Circadian Rhythm"/ or (shift$1 or post-shift$ or postshift$ or one-shift$ or two-shift$ or three-shift$ or circadian$). tw. 19. 17 and 18 20. 14 or 19 21. 4 and 20 22. ((shiftwork$ or shift-work$ or night-shift$ or nightshift$ or night work$ or nightwork$ or night-work$ or off-shift$ or night-call$1). ti. or (*Night Care/ma or exp *Work Schedule Tolerance/)) and health. ti. 23. or/21-22 24. 23 not ((animals/ or in vitro/) not (humans/ or exp persons/)) 25. limit 24 to "all child (0 to 18 years)" 26. limit 24 to "all adult (19 plus years)" 27. 25 not 26 28. 24 not 27 29. limit 28 to english language
Embase	1. exp cardiovascular disease/ or exp cardiovascular agent/ or exp cerebrovascular disease/ or cardiovascular risk/ or exp blood pressure/ or coronary risk/ or exp cardiovascular system/ or exp cardiovascular system examination/ or exp cardiovascular parameters/ or exp cardiovascular function/ or exp death/ or death certificate/ or morbidity/ or mortality/ or life table/ or vital statistics/ or "cardiovascular diseases and cardiovascular surgery". ec. 2. exp blood pressure/ or (blood pressure$ or hypertens$ or BP or SBP or DBP or diastolic$ or systolic$ or antihypertens$ or prehypertens$). mp. 3. (((hazard$ or cox) adj2 model$) or ((systolic$ or diastolic$) adj2 (dysfunction$ or function$)) or (arterial adj2 (occlusive or obstructive)) or (diabet$ adj2 (angiopat$ or microangiopat$)) or (ventric$ adj2 (dysfunction$ or function$ or rhythm$ or tachycardia$)) or actuarial$ or aortocoronar$ or angina or arrhythmi$ or arteriosclero$ or asystole$ or cad or cardi$ or carotid$ or cerebral$ or cerebro$ or chd or chf or coronary$ or cva$1 or or dead or death$ or died or dying or embol$ or fatalit$ or heart or ihd or infarct$ or isch?emi$ or kaplan meier$ or kaplan-meier$ or lethal$ or life table$ or lifetable$ or mi or morbid$ or mortalit$ or myocardi$ or stroke$1 or thrombol$ or thrombos$ or vascular$ or vasculatur$). mp. 4. or/1-3 5. ((on-call or oncall) and (duty or duties or hours or shift$1)). tw. 6. ((shift$1 or post-shift$ or postshift$ or one-shift$ or two-shift$ or three-

	shift$) adj5 (duty or duties)). tw. 7. ((shift$1 adj (system$1 or breaks or hour$)) or (hour$ adj shift$1)). tw. 8. (shiftwork$ or shift-work$ or night-shift$ or nightshift$ or night work$ or nightwork$ or night-work$ or off-shift$ or night-call$1). tw. 9. ((overnight or night$ or float$) adj5 (schedul$ or call or on-call or oncall)). tw. 10. ((alternating or work$ or schedule$ or rotating or backward-rotat$ or extended$ or forward-rotat$ or night$ or day-night$ or overnight$ or unconventional or roster$) adj3 (shift$1 or post-shift$ or postshift$ or one-shift$ or two-shift$ or three-shift$)). tw. 11. ((night$ adj2 (duty or duties or float$ or work$)) or (atypical adj (schedule$1 or shift$1 or hour$1)) or (hour$1 adj2 (float$ or work$))). tw. 12. (night and work$). hw. 13. ((roster$ or work or alternating or rotating or night$) adj1 schedul$). tw. 14. work schedule/ or shift worker/ or night work/ 15. or/5-14 16. (ergonomics or occupational or industrial). jw. not ((microbiology or physiology or hygiene). jw. or occupational exposure/ or expos$. ti. or (torque$ or cycling$). tw.) 17. occupational health and industrial medicine. ec. or occupational health/ or working time/ or occupational disease/ or personnel management/ or blue collar worker/ or industrial worker/ or worker/ 18. or/16-17 19. sleep disorder/ or sleep deprivation/ or circadian rhythm/ or "circadian rhythm sleep disorder"/ or (shift$1 or post-shift$ or postshift$ or one-shift$ or two-shift$ or three-shift$). tw. or circadian$. mp. 20. 18 and 19 21. ((shiftwork$ or shift-work$ or night-shift$ or nightshift$ or night work$ or nightwork$ or night-work$ or off-shift$ or night-call$1). ti. or (*work schedule/ or shift worker/ or *night work/)) and health. ti. 22. 15 or 20 23. 4 and 22 24. 21 or 23 25. 24 not ((exp "miscellaneous groups of organisms"/ or exp "in vitro study"/) not (human/ or exp "miscellaneous named groups"/)) 26. limit 25 to english language
Scopus or Science Citation Index Expanded (SCI-EXPANDED) or New Conference Proceedings Citation Index-	1. blood-pressure* or hypertens* or BP or SBP or DBP or diastolic* or systolic* or antihypertens* or prehypertens* 2. (arterial AND (occlusive or obstructive)) or (diabet* AND (angiopat* or microangiopat*)) or (ventric* AND (dysfunction* or function* or rhythm* or tachycardia*)) 3. aortocoronar* or angina or arrhythmi* or arteriosclero* or asystole* or cardi* or carotid* or cerebr* or coronar* or cva* or or embol* or heart* or

Science (CPCI-S) or BIOSIS previews	infarct* or ischaemi* or ischemi* or morbid* or mortalit* or myocardi* or stroke* or thrombo* or vascul* 4. OR/1-3 5. ((on-call or oncall) and (duty or duties or hours or shift*)) 6. ((shift* or post-shift* or postshift* or one-shift* or two-shift* or three-shift*) AND (duty or duties)) 7. "shift* system*" OR "shift* breaks" OR shift-hour* OR "hour* shift*" OR shift-system* 8. shiftwork* or shift-work* or night-shift* or nightshift* or "night work*" or nightwork* or night-work* or night-call* 9. ((overnight or night* or float*) AND (schedul* or call or on-call or oncall)) 10. ((worker* or rotating or night* or day-night* or overnight* or roster*) AND (shift* or post-shift* or postshift* or one-shift* or two-shift* or three-shift*)) 11. night-duty OR night-duties OR night-float* 12. work-schedul* OR alternating-schedul* OR rotating-schedul* OR night-schedul* 13. OR/5-12 14. ((shiftwork* or shift-work* or night-shift* or nightshift* or night work* or nightwork* or night-work* or night-call*) AND (death* OR health* OR metabolic*)) 15. ((OR/1-3) AND (OR/5-12)) OR 14 LIMITS LANGUAGES = (ENGLISH)
Google Scholar	"shift work" AND (coronary OR cardiovascular OR myocardial OR ischemic OR infarction OR infarct OR stroke OR cerebrovascular OR ischemia OR vascular OR angina OR mortality OR morbidity OR death OR dead OR chd OR cad OR ihd) “shiftwork” AND (coronary OR cardiovascular OR myocardial OR ischemic OR infarction OR infarct OR stroke OR cerebrovascular OR ischemia OR vascular OR angina OR mortality OR morbidity OR death OR dead OR chd OR cad OR ihd) “rotating work” AND (coronary OR cardiovascular OR myocardial OR ischemic OR infarction OR infarct OR stroke OR cerebrovascular OR ischemia OR vascular OR angina OR mortality OR morbidity OR death OR dead OR chd OR cad OR ihd) “night work” AND (coronary OR cardiovascular OR myocardial OR ischemic OR infarction OR infarct OR stroke OR cerebrovascular OR ischemia OR vascular OR angina OR mortality OR morbidity OR death OR dead OR chd OR cad OR ihd)

	“evening work” AND (coronary OR cardiovascular OR myocardial OR ischemic OR infarction OR infarct OR stroke OR cerebrovascular OR ischemia OR vascular OR angina OR mortality OR morbidity OR death OR dead OR chd OR cad OR ihd)

Appendix E. Data abstraction form

Shift work and cardiovascular outcomes – Data Abstraction Form

Reviewer:	Date:

I STUDY FEATURES

A) Study Design

- ☐ Case-control
- ☐ Cohort
- ☐ Cross-sectional
- ☐ Ecological
- ☐ Other (please specify)

B) Data collection

- ☐ Prospective
- ☐ Retrospective

II SAMPLE CHARACTERISTICS

A) Geographic locale

B) Industry(s)

C) Accrual interval (dd/mm/yyyy – dd/mm/yyyy)

D) Follow up interval (dd/mm/yyyy – dd/mm/yyyy)

E) Inclusion criteria

F) Exclusion criteria

G) Number of workers screened/approached

H) Final sample size (after selection criteria)

I) Comparison groups for statistical analyses

Designation of group	Sample size of group

J) Demographics (overall sample)

Demographic data	**Yes**	**No**	**Unknown**	**Mean (SD) or Median (IQR/range) or proportion or other point estimate with measure of dispersion**
Age	☐	☐	☐	
Sex (n, % Male)	☐	☐	☐	
Education level	☐	☐	☐	
Socioeconomic status	☐	☐	☐	
Marital status	☐	☐	☐	
Smoking status	☐	☐	☐	
Other (please specify) A. B.				

Source of information for the sample

☐ Industry records
☐ Administrative database
☐ Survey
☐ Questionnaire
☐ Registry
☐ Other (please specify)
☐ Interview
☐ Census data
☐ Routine medical records
☐ Government/labour bureau

K) Details of exposure

1. How was shift work defined? (be specific)

Further details on shift work exposure	**Yes**	**No**	**Unknown**
Irregular working hours	☐	☐	☐
Night work	☐	☐	☐
Early morning work	☐	☐	☐
Evening work	☐	☐	☐
Rotating shifts	☐	☐	☐
Other (please specify)			
Total number of years of shift work			

2. Mean duration of shift work

3. Shift work classification:
   - Night work
   - Evening work
   - Irregular work
   - Rotating work
   - Unspecified Shift work

L) Details of outcome

1. How many outcomes of interest were assessed?

Outcome	**Definition**

2. Source of information

- ☐ Industry records
- ☐ Administrative database
- ☐ Survey
- ☐ Questionnaire
- ☐ Patient registry
- ☐ Other (please specify)
- ☐ Interview
- ☐ Census data
- ☐ Routine medical records
- ☐ Government/labour bureau

III ANALYSIS AND RESULTS

A) Confounding

1. Which variables were proposed to be confounders?

2. Which variables were adjusted for in the analyses?

3. Which analytic method was used to control for confounding?

B) **Analyses**

1. Which effect measure was reported?

☐ Hazard Ratio
☐ Rate Ratio
☐ Risk Ratio
☐ Odds Ratio
☐ Standardized Mortality/Morbidity Ratio
☐ Other (please specify)

Outcome of interest	Years of follow up (cohorts only)	Events in shift work group (n_1)	Size of the shift work group	Events in non-shift work group (n_2)	Size of the non-shift work group	Crude effect estimate (95% CI or P value)	Adjusted Estimate (95% CI or P value)	Variables adjusted

2. **Healthy worker bias**

Did the authors account for healthy worker bias? Yes ☐ No ☐

If **Yes** – How was this analysis performed? (Give brief details)

3. **Dose response relationship**

How was exposure (shift work) treated in this analysis?
☐ Continuous ☐ Categorical

Comparison group	Crude effect estimate 95% CI or P value	Adjusted estimate 95% CI or P value	Variables adjusted for

4. **Subgroup analysis**

Subgroup	Operational definition	*A priori* inclusion? (Y/N/Unclear)	Crude effect estimate (95% CI or P value)	Adjusted effect estimate (95% CI or P value)	Formal test of interaction? Y/N/Unclear

5. Describe any other analyses that were performed to assess the effect of exposure on the outcome. Please provide crude and adjusted effect estimate with 95% CI or P values for each such analysis.

6. How many separate analyses were reported in the manuscript?

7. Did the authors adjust or otherwise account for multiple hypotheses testing? If so how?

V MISCELLANEOUS

A) Funding Source

☐ Private ☐ Public ☐ Mixed
☐ Not specified ☐ Unclear

B) Additional Comments of the reviewer

Appendix F. Downs and Black checklist for study quality

Reporting

l. *Is the hypothesis/aim/objective of the study clearly described?*

yes	1
no	0

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods section?*
   If the main outcomes are first mentioned in the Results section, the question should be answered no.

yes	1
no	0

3. *Are the characteristics of the patients included in the study clearly described?*
   In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

yes	1
no	0

4. *Are the interventions of interest clearly described?*
   Treatments and placebo (where relevant) that are to be compared should be clearly described.

yes	1
no	0

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*
   A list of principal confounders is provided.

yes	2
partially	1
no	0

6. *Are the main findings of the study clearly described?*
   Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).

yes	1
no	0

7. *Does the study provide estimates of the random variability in the data for the main outcomes?*
   In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

yes	1
no	0

8. *Have all important adverse events that may be a consequence of the intervention been reported?*
   This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible

adverse events is provided).

yes	1
no	0

9. *Have the characteristics of patients lost to follow-up been described?*
   This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

yes	1
no	0

10. *Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*

yes	1
no	0

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*
    The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

yes	1
no	0
unable to determine	0

12. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*
    The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

yes	1
no	0
unable to determine	0

13. *Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?*
    For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

yes	1
no	0

unable to determine	0

Internal Validity - bias

14. *Was an attempt made to blind study subjects to the intervention they have received?*
    For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

yes	1
no	0
unable to determine	0

15. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

yes	1
no	0
unable to determine	0

16. *If any of the results of the study were based on "data dredging", was this made clear?*
    Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported) then answer yes.

yes	1
no	0
unable to determine	0

17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?*
    Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

yes	1
no	0
unable to determine	0

18. *Were the statistical tests used to assess the main outcomes appropriate?*
    The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

yes	1
no	0
unable to determine	0

19. *Was compliance with the interventions reliable?*
    Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

yes	1
no	0
unable to determine	0

20. *Were the main outcome measures accurate (valid and reliable)?*
For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

yes	1
no	0
unable to determine	0

Internal Validity - confounding (selection bias)

21. *Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?*
For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.

yes	1
no	0
unable to determine	0

22. *Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?*
For a study which does not specific the time period over which patients were recruited, the question should be answered as unable to determine.

yes	1
no	0
unable to determine	0

23. *Were study subjects randomised to intervention groups?*
Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.

yes	1
no	0
unable to determine	0

24. *Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*
All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

yes	1
no	0
unable to determine	0

25. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*
This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or

confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

yes	1
no	0
unable to determine	0

26. *Were losses of patients to follow-up taken into account?*
If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

yes	1
no	0
unable to determine	0

Power

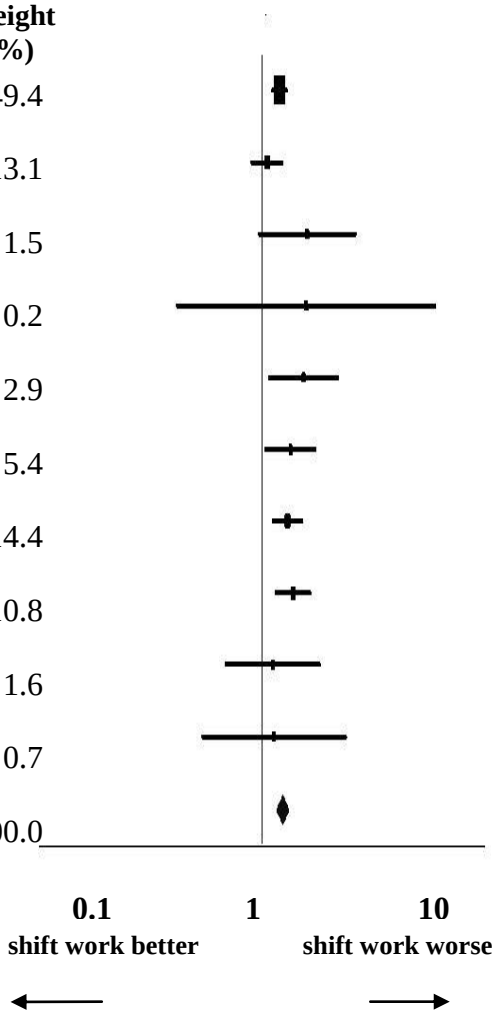
27. *Did the studies have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?*
Sample sizes have been calculated to detect a difference of x% and y%.

	Size of *smallest* intervention group	
A	$<n_1$	0
B	n_1-n_2	1
C	n_3-n_4	2
D	n_5-n_6	3
E	n_7-n_8	4
F	n_8 +	5

Appendix G. Forest plots of meta-analyses of observational studies investigating the association between shift work and cardiovascular outcomes

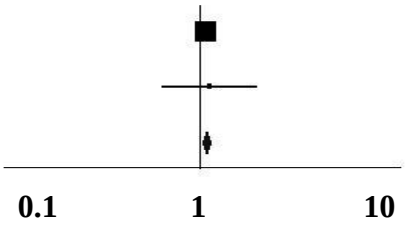
1. Myocardial Infarction

Study	Risk Ratio (95% CI)	Weight (%)
Alfredsson et al., 2004	1.20 (1.09-1.31)	49.4
Babisch et al., 2005	1.05 (0.89-1.25)	13.1
Falger and Schouten, 1992	1.59 (0.96-2.64)	1.5
Fukuoka et al., 2005	1.57 (0.41-5.98)	0.2
Haupt et al., 2008	1.53 (1.06-2.21)	2.9
Kawachi et al., 1995	1.34 (1.02-1.76)	5.4
Knutsson et al., 1999	1.30 (1.10-1.53)	14.4
Laugsand et al., 2011	1.37 (1.14-1.66)	10.8
Liu and Tanaka, 2002	1.12 (0.68-1.83)	1.6
Netterstrom et al., 1999	1.13 (0.54-2.39)	0.7
Total (I^2 = 0%)	**1.23 (1.15-1.31)**	100.0



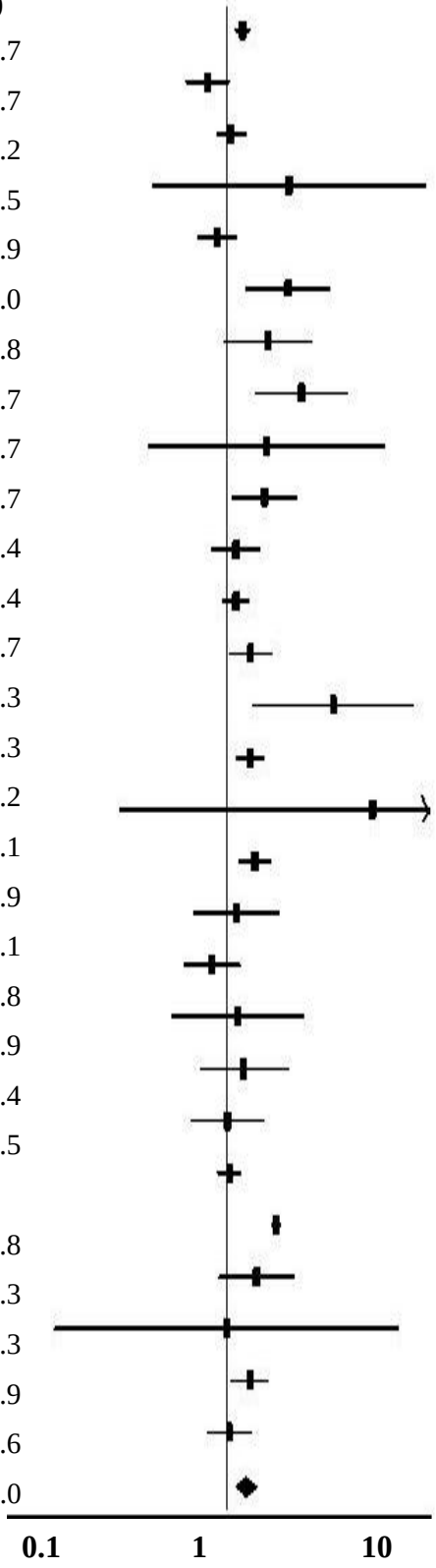
2. Ischemic stroke

Study	Risk Ratio (95% CI)	Weight (%)
Brown et al., 2009	1.05 (1.01-1.09)	99.3
Hermansson et al., 2007	1.08 (0.69-1.70)	0.7
Total (I^2 = 0%)	**1.05 (1.01-1.09)**	100.0



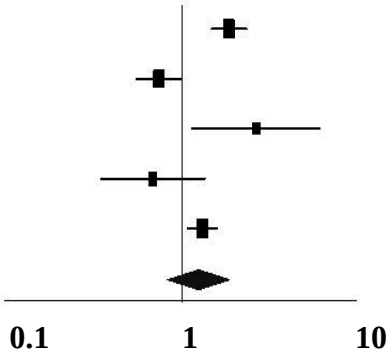
3. Coronary events

Study	Risk Ratio (95% CI)	Weight (%)
Alfredsson et al., 2004	1.20 (1.09-1.31)	5.7
Allesoe et al., 1985	0.81 (0.63-1.04)	4.7
Babisch et al., 2005	1.05 (0.89-1.25)	5.2
Biggi et al., 2008	2.02 (0.43-9.40)	0.5
Boggild et al., 1999	0.90 (0.72-1.13)	4.9
Ellingsen et al., 2007	1.99 (1.23-3.22)	3.0
Falger and Schouten, 1992	1.59 (0.96-2.64)	2.8
Fujino et al., 2006	2.32 (1.37-3.94)	2.7
Fukuoka et al., 2005	1.57 (0.41-5.98)	0.7
Haupt et al., 2008	1.53 (1.06-2.21)	3.7
Hublin et al., 2010	1.11 (0.84-1.47)	4.4
Karlsson et al., 2005	1.11 (0.95-1.30)	5.4
Kawachi et al., 1995	1.31 (1.02-1.68)	4.7
Knutsson et al., 1986	3.32 (1.33-8.26)	1.3
Knutsson et al., 1999	1.30 (1.10-1.53)	5.3
Koller, 1983	5.17 (0.30-89.43)	0.2
Laugsand	1.37 (1.14-1.66)	5.1
Liu and Tanaka, 2002	1.12 (0.68-1.83)	2.9
McNamee et al., 1996	0.85 (0.61-1.18)	4.1
Netterstrom et al., 1999	1.13 (0.54-2.39)	1.8
Rafnsson and Gunnarsdottir, 1990	1.21 (0.74-1.98)	2.9
Steenland and Fine, 1996	1.01 (0.67-1.53)	3.4
Taylor and Pocock (re-analyzed by Knutsson et al., 2004)	1.03 (0.90-1.18)	5.5
Tuchsen, 1993	1.74 (1.65-1.84)	5.8
Tuchsen et al., 2006	1.40 (0.91-2.15)	3.3
Vertin, 1978	1.00 (0.14-6.96)	0.3
Virkunen et al., 2006	1.30 (1.04-1.62)	4.9
Yadegarfar and McNamee, 2009	1.03 (0.80-1.33)	4.6
Total (I^2 = 85%)	**1.24 (1.10-1.39)**	100.0



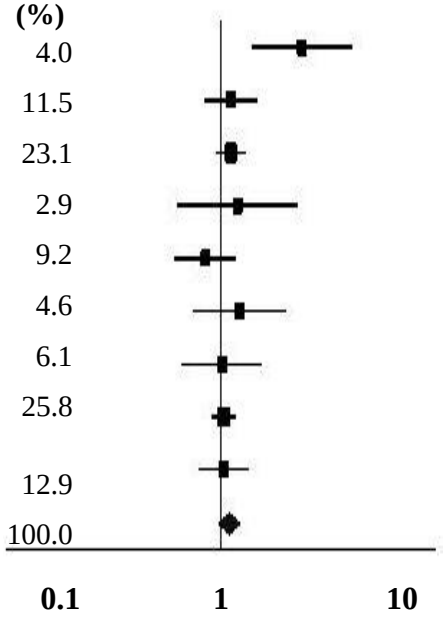
4. Cardiovascular events

Study	Risk Ratio (95% CI)	Weight (%)
Ellingsen et al., 2007	1.89 (1.47-2.44)	24.4
Hublin et al., 2010	0.72 (0.53-1.00)	23.2
Koller, 1983	2.73 (1.12-6.64)	12.4
Taylor et al., 1972	0.67 (0.32-1.37)	15.1
Tuchsen et al., 2006	1.31 (1.06-1.62)	25.0
Total (I^2 = 85%)	**1.24 (0.81-1.89)**	100.0



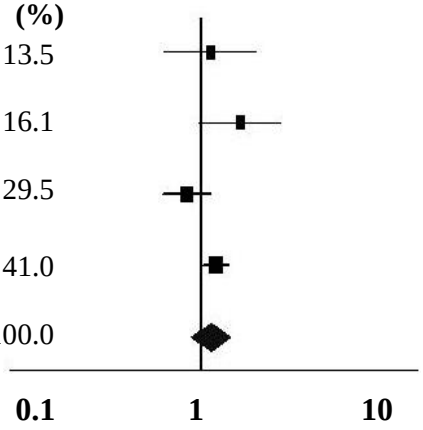
5. Coronary mortality

Study	Risk Ratio (95% CI)	Weight (%)
Fujino et al., 2006	2.32 (1.37-3.94)	4.0
Hublin et al., 2010	1.11 (0.84-1.47)	11.5
Karlsson et al., 2005	1.11 (0.95-1.30)	23.1
Kawachi et al., 1995	1.19 (0.63-2.24)	2.9
McNamee et al., 1996	0.85 (0.61-1.18)	9.2
Rafnsson and Gunnarsdottir, 1990	1.21 (0.74-1.98)	4.6
Steenland and Fine, 1996	1.01 (0.67-1.53)	6.1
Taylor and Pocock (re-analyzed by Knutsson et al., 2004)	1.03 (0.90-1.18)	25.8
Yadegarfar and McNamee, 2008	1.03 (0.80-1.33)	12.9
Total (I^2 = 29%)	**1.08 (0.97-1.21)**	100.0



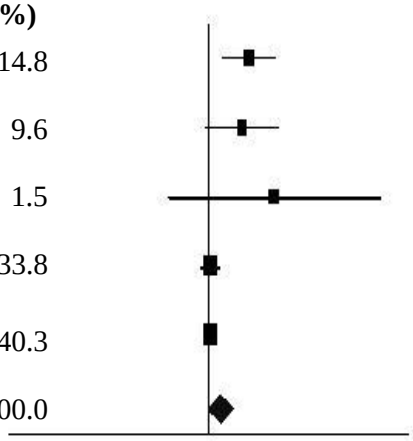
6. Cerebrovascular death

Study	Risk Ratio (95% CI)	Weight (%)
Fujino et al., 2006	1.12 (0.66-1.91)	13.5
Karlsson et al., 2005	1.56 (0.97-2.50)	16.1
Taylor and Pocock (re-analyzed by Knutsson et al., 2004)	0.86 (0.65-1.12)	29.5
Virtanen and Notkola, 2002	1.19 (1.01-1.40)	41.0
Total (I^2 = 52%)	**1.12 (0.89-1.40)**	100.0



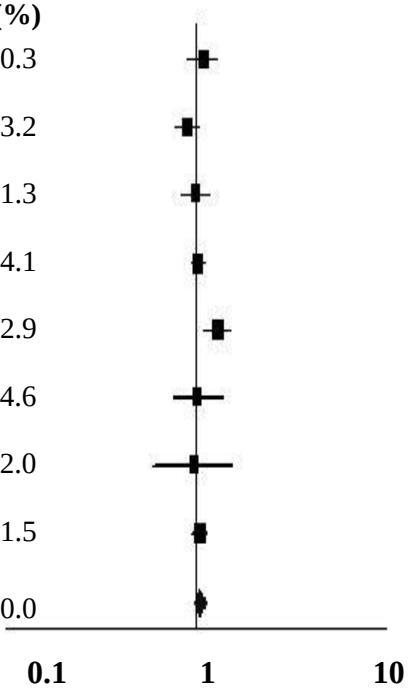
7. Cardiovascular mortality

Study	Risk Ratio (95% CI)	Weight (%)
Fujino et al., 2006	1.59 (1.16-2.18)	14.8
Kawachi et al., 1995	1.46 (0.95-2.24)	9.6
Tarumi, 1997	2.14 (0.63-7.29)	1.5
Taylor and Pocock (re-analyzed by Knutsson et al., 2004)	1.02 (0.90-1.15)	33.8
Virtanen and Notkola, 2002	1.02 (0.96-1.08)	40.3
Total (I^2 = 65%)	**1.14 (0.98-1.32)**	100.0



8. All cause mortality

Study	Risk Ratio (95% CI)	Weight (%)
Akerstedt et al., 2004	1.08 (0.90-1.31)	10.3
Boggild et al., 1999	0.90 (0.77-1.06)	13.2
Fujino et al., 2006	0.98 (0.82-1.17)	11.3
Karlsson et al., 2005	1.02 (0.93-1.11)	24.1
Kawachi et al., 1999	1.29 (1.10-1.52)	12.9
Rafnsson and Gunnarsdottir, 1990	1.01 (0.74-1.38)	4.6
Tarumi, 1997	0.96 (0.59-1.56)	2.0
Taylor and Pocock (re-analyzed by Knutsson et al., 2004)	1.03 (0.93-1.14)	21.5
Total (I^2 = 36%)	**1.04 (0.97-1.11)**	100.0



Appendix H. Data on covariates for meta-regression analyses

(Part 1)

study	year of accrual	duration of follow-up	effective sample size	% shift workers	mean age	% females
alfredsson	1975	1	958096	NA	42.00	NA
allesoe	1993	15	12116	NA	51.00	1
babisch	1998	NA	4115	0.23	56.52	0.26
biggi	1976	32	468	0.66	45.49	0
boggild	1970	22	5207	0.22	48.13	0
ellingsen	1972	31	2562	0.25	47.00	0
falger	1980	NA	325	0.68	51.13	0
fujinio	1988	15	16785	0.12	49.47	0
fukuoka	2002	NA	94	0.11	51.35	0.02
haupt	1997	67.17	2510	0.28	61.72	0.5
hublin	1975	22	18609	0.11	40.20	0.51
karlsson	1940	50	5442	0.43	26.27	0
kawaachi	1976	4	79109	0.59	54.50	1
knutsson 86	1968	15	504	0.78	39.89	0
knutsson 99	1992	NA	4571	0.14	55.00	0.31
koller	1978	32.85	267	0.75	33.70	0
liu	1996	NA	705	0.10	56.87	0
mcnamee	1950	NA	886	0.67	38.70	0
netterstrom	1991	NA	252	0.15	50.34	0
rafnsson	1954	32	603	0.35	NA	0
steenland	1951	NA	889	0.24	NA	0
taylor/knutsson	1956	13	8048	0.52	59.50	0
tuchsen 93	1981	4	366055	0.33	39.50	0
tuchsen 06	1991	12	5455	0.17	35.59	0.48
vertin	1971	3	200	0.50	49.89	0
virkunen	1982	13	1804	0.37	52.65	0
yadegarfar	1950	NA	1270	0.55	35.75	0
laugsand	1995	11.4	33123	0.15	49.45	0.55

(Part 2)

study	% blue collar workers	rotating shifts	MI	source of outcome	sample risk	Control group	adjusted for confounders
alfredsson	NA	N	Y	2	0.13	general	Y
allesoe	0	Y	N	2	0.32	day	Y
babisch	NA	N	Y	1	45.71	day	Y
biggi	1	N	N	1	0.07	day	N
boggild	0.74	N	N	2	0.88	day	Y
ellingsen	NA	Y	N	1	0.08	day	N
falger	NA	N	Y	1	40.92	day	Y
fujinio	0.53	Y	N	2	0.04	day	Y
fukuoka	0.17	N	Y	1	50.00	day	Y
haupt	NA	N	Y	1	0.16	day	Y
hublin	0.49	N	N	2	0.21	day	Y
karlsson	1	Y	N	2	0.40	day	Y
kawaachi	0	Y	N	1	0.10	day	Y
knutsson 86	1	Y	N	1	0.69	day	Y
knutsson 99	NA	N	Y	1	43.16	day	Y
koller	1	Y	N	1	0.14	day	N
liu	0.36	Y	Y	1	36.88	day	N
mcnamee	1	Y	N	2	50.00	day	Y
netterstrom	0.37	N	Y	1	30.16	day	Y
rafnsson	0.83	N	N	2	0.80	general	Y
steenland	1	N	N	2	17.44	day	Y
taylor/knutsson	1	Y	N	2	0.53	general	Y
tuchsen 93	NA	N	N	2	0.37	general	Y
tuchsen 06	NA	N	N	2	0.17	day	Y
vertin	1	N	N	1	0.67	day	N
virkunen	0.71	N	N	2	1.80	day	Y
yadegarfar	1	N	N	2	50.00	day	Y
laugsand	NA	N	Y	1	0.15	day	Y

Source of outcome: 1 = primary and 2 = secondary
Control group: general = general population and day = day workers

(Part 3)

study	# of confounders	adjusted for SES	adjusted for smoking	time dependence	Downs and Black score	power score (1-β)	duration of shift work (years)
alfredsson	1	N	N	Y	0.66	0.95	NA
allesoe	10	Y	Y	Y	0.71	NA	NA
babisch	10	Y	Y	N	0.59	0.06	NA
biggi	0	N	N	N	0.41	0.06	NA
boggild	7	Y	Y	Y	0.86	1	10.1
ellingsen	0	N	N	N	0.41	0.74	NA
falger	2	N	N	N	0.52	0.58	NA
fujinio	10	Y	Y	Y	0.66	0.65	NA
fukuoka	2	N	N	N	0.48	0.52	NA
haupt	3	N	Y	Y	0.66	0.83	13.2
hublin	16	Y	Y	Y	0.75	NA	12.19
karlsson	1	N	N	Y	0.69	1	23.1
kawaachi	15	Y	Y	Y	0.79	0.88	3.99
knutsson 86	1	N	N	Y	0.66	0.06	15.24
knutsson 99	3	Y	Y	N	0.83	1.00	NA
koller	0	N	N	N	0.45	0.62	7.88
liu	2	N	N	N	0.52	0.05	NA
mcnamee	7	N	Y	N	0.59	0.29	3.7
netterstrom	2	N	N	N	0.48	0.08	NA
rafnsson	1	N	N	Y	0.59	1.00	7.61
steenland	3	N	N	N	0.52	0.06	NA
taylor/knutsson	1	N	N	Y	0.69	1.00	10
tuchsen 93	1	N	N	Y	0.59	1.00	NA
tuchsen 06	16	N	Y	Y	0.86	1.00	NA
vertin	0	N	N	N	0.34	0.05	NA
virkunen	4	N	Y	Y	0.62	0.75	NA
yadegarfar	8	Y	Y	N	0.66	0.11	7.55
laugsand	10	Y	Y	Y	0.67	NA	NA

Abbreviations: Y yes, N no, NA not available

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