Review

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Shift work and the risk of cardiovascular disease. A systematic review and meta-analysis including dose–response relationship

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Objectives The aim of this review was to assess the risk of cardiovascular disease (CVD) events associated with shift work and determine if there is a dose–response relationship in this association.

Method Electronic databases (PubMed, Scopus, and Web of Science) were searched for cohort or case–control control study designs in any population, reporting exposure to shift work as the main contributing factor to estimate CVD risk. For each study, adjusted relative risk (RR) ratios and 95% confidence intervals (CI) were extracted, and used to calculate the pooled RR using random-effect models. Meta-regression analysis was conducted to explore potential heterogeneity sources. Potential non-linear dose–response relationships were examined using fractional polynomial models.

Results We included 21 studies with a total of 173 010 unique participants. The majority of the studies were ranked low-to-moderate risk of bias. The risk of any CVD event was 17% higher among shift workers than day workers. The risk of coronary heart disease (CHD) morbidity was 26% higher (1.26, 95% CI 1.10–1.43, I^2= 48.0%). Sub-group analysis showed an almost 20% higher risk of CVD and CHD mortality among shift workers than those who did not work shifts (1.22, 95% CI 1.09–1.37, I^2= 0% and 1.18, 95% CI 1.06–1.32 I^2=0%; respectively). After the first five years of shift work, there was a 7.1% increase in risk of CVD events for every additional five years of exposure (95% CI 1.05–1.10). Heterogeneity of the pooled effect size (ES) estimates was high (I^2=67%), and meta-regression analysis showed that sample size explained 7.7% of this.

Conclusions The association between shift work and CVD risk is non-linear and seems to appear only after the first five years of exposure. As shift work remains crucial for meeting production and service demands across many industries, policies and initiatives are needed to reduce shift workers' CVD risk.

Key words coronary heart disease; CVD; effect size; shift worker.

Shift workers play a vital role in maintaining the 24/7 operations in many production, healthcare, and service delivery industries. It is estimated that 15–30% of workers are employed as rotational shift workers, which includes working day, afternoon and night shifts (1). These types of work schedules alter shift workers' circadian rhythms, which may affect glucose and lipid metabolism, inflammation, and autonomic nervous system regulation, increasing the risk of atherosclerosis, dyslipidemia and insulin resistance (2, 3). In addition, there is a higher prevalence of inactivity, smoking, excess weight, and poor diet among shift workers compared to those who do not work shifts (4). These factors put shift workers at an increased risk of non-communicable diseases, including cardiovascular disease (CVD) (5, 6).

The most recent meta-analysis of the relationship between shift work and CVD risk was published in 2012; it reported that shift workers were at 24% higher risk of coronary events [95% confidence interval (CI) 1.10–1.39] than non-shift workers (7). However, the estimated pooled effects presented in that study did not consider differences in the duration of shift work among

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participants in each study. Two other meta-analyses have shown a dose–response relationship between shift work and cancer (8, 9); one found an 11% increased risk of colon cancer for every five years of shift work (8). The other study showed a 13% increased risk of breast cancer for each additional 500 night shifts (9). It is not known whether similar associations exist for CVD.

The objective of this meta-analysis was, therefore, to update the evidence on the relationship between shift work exposure and CVD mortality and morbidity risk. Furthermore, we aimed to determine whether there is a dose–response relationship between years of shift work and CVD risk.

Methods

Search strategy and selection criteria

We followed the framework proposed by the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) group for design, research strategy, analysis and reporting (10). Ethical approval was not applicable to this study design as the data extracted and analyzed were not from single participants but from aggregated published data. Peer-review publications were searched using three major databases: PubMed, Scopus, and Web of Science. All searches were performed using title/abstract/keywords fields combining shift work and CVD terms. Based on the WHO criteria (11), we considered CVD as a group of disorders of the heart and blood vessels, including coronary heart diseases (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. In the PubMed database, we used MeSH terms to ensure all CVD outcomes were included. MeSH terms used were "heart diseases [mh]" and "vascular diseases [mh]". Truncated wildcard terms for major CVDs, as described by WHO criteria (eg, card* OR vasc* OR myocar* OR pericar*), were used in the other two databases. For shift work keywords, we included terms similar to those used in a previous systematic review on shift work and metabolic risk factors:(12) "shift work" OR "shiftwork" OR "irregular hours" OR "rotating shift" OR "rotating hours" (complete list of all search term and strategies available on request). The search was limited to longitudinal and case–control studies published between 2006 and 2016. This time period was selected in line with our aims to update the previous meta-analysis by Vyas et al (7), in which the majority of studies (21/32) were published before 2006. Reference lists of the papers included in previous meta-analyses and systematic reviews were also scanned for relevant studies.

Two reviewers scanned titles and abstracts independently to decide on article eligibility. To be eligible, a study had to meet the previously agreed inclusion/exclusion criteria: (i) longitudinal or case–control control study design; (ii) includes a measure of shift work defined as permanent night shift or rotational shift, or a combination of terms to indicate work arrangements that differ from standard hours (07:00/08:00–17:00/18:00 hours) (13); (iii) provides an estimate of risk for a CVD outcome, either for morbidity or mortality; (iv) describes exposure to shift work as the main contributing factor to CVD risk estimates. Studies in which shift work exposure was a secondary factor to insomnia, work stress, etc. were excluded; (v) studies presenting only metabolic syndrome or CVD marker outcomes (eg, hypertension, insulin-resistance) were excluded, as the focus of this review was on CVD outcomes.

After selecting studies based on title/abstract, a full-text scan of the remaining studies was performed. Disagreements on study selection were discussed between the two reviewers, with the consultation of a third reviewer to reach consensus. After fulltext review, 21 articles met all selection criteria and were included in the meta-analysis.

Data extraction

Two reviewers independently extracted data from each study. This included information on author/year, study design, follow-up duration/years, CVD outcome, sample size, age and sex, industry in which participants worked and/or cohort name (if ongoing cohort study), definition and assessment of shift work, duration of exposure to shift work (if reported), and variables used in the adjusted model for risk estimate. If an estimate of all-cause mortality was provided in addition to CVD morbidity/mortality outcomes, this was also recorded. Risk estimates were extracted for both crude and adjusted models of odds ratio, relative risk, hazard ratio or beta-coefficient of risk. For each adjusted estimate, we also extracted and reported variables that were included in the model. When provided, we included this estimate, adjusted for all the variables described in the methods section of that particular study.

Risk of bias assessment

For the risk of bias assessment, we selected a validated tool, which was used in a previous meta-analysis of the results of longitudinal and cohort studies of the effects of shift-work on cancer risk (14). This tool assesses critical sources of bias such as shift work exposure definition and assessment, using criteria suggested by the World Health Organization (13). In line with the risk of bias assessment conducted by Ijaz et al (14), we consid-

ered the following major domains of bias: (i) exposure definition, (ii) exposure assessment, (iii) reliability of assessments, (iv) confounding, and (v) analysis methods (research-specific bias). The following criteria were also considered as minor domains of bias: (ia) blinding of assessors, (iia) attrition, (iiia) selective reporting, (iva) funding, and (va) conflict of interest. Each criterion was rated as high, low, or unclear risk of bias, as described in supplementary table S1 (www.sjweh.fi/show_abstract.php?abstract_id=3700). Based on these ratings, we classified studies as low (if all major domains and >2 minor domains scored low risk); moderate (if 4 major domains and ≥2 minor domains scored low risk); or high (if <4 major domains scored low risk) risk of bias. Risk of bias assessment was performed independently by the two reviewers, who discussed and resolved eventual disagreements on risk of bias assessment.

Data management and statistical analyses

Risk estimates, including risk ratios, odds ratios or hazard risks, and their respective standard errors or 95% confidence intervals (95% CI) were extracted, using data from non-shift workers (ie, those who only worked usual daytime hours, 08:00–17:00 hours) as the reference group in all studies. When a study provided more than one risk estimate, estimates with the highest level of adjustment for covariates were selected. When analyses for men and women were calculated separately, two independent estimates were included in the meta-analysis. If the study presented estimates for more than one group of work schedules, as sub-groups of shift work (eg, rotational, fixed night), only estimates from the major category were included (eg, fixed night as a subgroup of "shift work"). If the exposure groups presented were independent, then estimates for both groups were included.

First, we conducted a "non-exposure versus exposure" meta-analysis, with shift work as the exposure group. As some studies had more than one exposure group, we included the risk estimates from the most representative group. For those studies with sub-groups based on years of shift work, we included data from cumulative estimates wherever possible. If no cumulative estimate was available, or we were unable to calculate it, we included data from the group with the highest number of years of shift work exposure. Risk estimates were used to calculate the pooled effect sizes (ES) using random-effects models, for the association between shift work and CVD overall risk, CVD mortality and morbidity risk.

Sub-group analyses were conducted with data from studies of "coronary heart disease - CHD morbidity" (morbidity outcomes that were cardiac-related such as myocardial infarction, ischemic disease), "other CVDs morbidity" (estimates for cardiovascular or circulatory disease but not limited to the heart), and "mortality" (estimates for both CVD mortality and all-cause mortality). Another sub-group analysis assessed shift work effect on "mortality" risk by type (CHD mortality, IHD mortality, circulatory diseases mortality, and CVD mortality). These were assessed separately to avoid double counting of estimates from the same study.

Heterogeneity was assessed using the I-squared test. Sensitivity analyses were conducted to assess the robustness of the data and to explore potential sources of heterogeneity. The first sensitivity analysis included univariate meta-regression by: type of outcome (CHD, other CVD, mortality), sex, type of industry where participants worked (eg, hospital, municipal workers, chemical industry), study design (longitudinal, case–control), age of the cohort (<50, >50 years old), sample size (> or <10 000), and overall risk of bias (low, moderate, high). A second sensitivity analysis was conducted for those items in the risk of bias assessment tool that scored "high risk", to explore their potential contributions to over/underestimation of results. Funnel plots and the Egger test were used to evaluate publication bias.

Following these analyses, we conducted a dose–response meta-analysis (15), using data from studies that presented a dose–response analysis in their results (N=5) (16–20). The level of exposure to shift work for each category was assigned to the corresponding risk estimate for each study using the midpoint between the lowest and highest limit for each category. The potential non-linear dose–response relationship was analyzed by fractional polynomial models (21). The best fitting model was defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for non-linearity (22). All analyses were conducted using Stata v12.1 (StataCorp, College Station, TX, USA).

Results

The results of the search process are shown in figure 1. After removal of duplicates, the literature search retrieved 488 articles. Of these, 57 fulltexts were reviewed, and 21 articles were found to be eligible for inclusion and data extraction.

Study characteristics

The 21 studies included a total of 362 591 participants. Three studies met the screening criteria, but were subsequently excluded from the meta-analysis. One of these had a cohort design, but only presented cross-sectional data (23), while two others provided risk estimates in

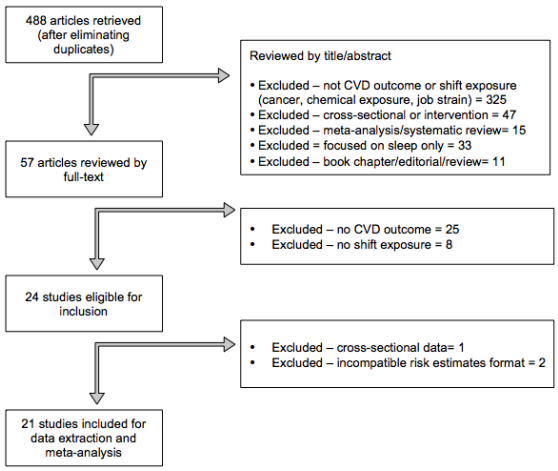

Figure 1. Flow diagram of literature search and selection of the included studies in the meta-analysis.

beta-coefficient formats only (24, 25). The latter two authors were contacted to request data in relative risk or odds ratio format, but no responses were received.

Characteristics of the included studies are shown in table 1, grouped according to the main outcomes. The majority were prospective cohort studies (N=15), while the remainder were case–control studies (N= 7). For cohort studies, the follow-up period ranged from 11–38 years. Data were from European cohorts, the USA, Asia and Middle East. Sample size ranged from 99–80 108 participants and participants' age from 36.1–66.3 years. Five studies had only female participants, while the rest had either only males or both genders. Almost half the studies (N=10) did not report the occupation of participants or included employees from different sectors indistinctively. In contrast, four studies focused on nurses and four included chemical and fuel industry workers only.

Definition and measure of exposure to shift work

Shift work was defined differently across studies. The majority described it as a work schedule in which day and night shifts alternate (19, 20, 26–31), with a specific rotation (32) or a minimum number of nights per week or month (16–18, 33). Other studies considered doing long working hours or weekend work as shift work (34, 35). Two studies did not provide a definition of shift work (36, 37), while others limited inclusion to fixed night shift workers (38–40), or considered shift work as any type of work schedule other than fixed day-only work (41).

Risk of bias assessment

One third of the cohort studies were ranked as high risk of bias, while half the case–control studies were at high risk of bias. In most cases, the overall high risk of bias was attributable to the definition of shift work exposure and assessment (criteria 1 and 2, table 2). These studies reported only one aspect of the shift work definition described by the International Agency for Research on Cancer (IARC) (13) or used one question to assess shift work status (eg, "Do you work shifts? Yes/no"), without providing information on duration of exposure and/or shift system (26–28, 35–38, 41). A majority of studies did not report on (ia) blinding of assessors and (iia) attrition, and for this reason these items were scored as "unclear" (table 2).

Effect of shift work on CVD events

As shown in figure 2, shift work was associated with an overall increased risk of any CVD events (ES:1.17, 95% CI 1.09–1.25, I^2= 67.0%). The subgroup analysis of studies with CHD and ischemic heart disease morbidity estimated significantly increased risks for CHD morbidity (ES: 1.26, 95% CI 1.10–1.43, I^2= 58.2%), but there was no significant association between shift work and "other CVD morbidity" (ES: 1.04, 95% CI 0.96–1.14 I^2=48%). Likewise, the risk of mortality seemed to be increased in shift workers, but this result did not reach significance (ES: 1.13, 95% CI 0.99–1.29, I^2=55.6%). However, a sub-group analysis including only mortality estimates, and stratified by type of mortality, showed that there were significant risks of CHD and any CVD mortality (ES: 1.18, 95% CI 1.06–1.32, I^2=0% and ES: 1.22, 95% CI 1.09–1.37, I^2=0%; respectively) (see figure S5, www.sjweh.fi/show_abstract.php?abstract_id=3700)

Dose-response effect of shift work on CVD disease risk

The results of the dose–response relationship analysis are shown in figure 3. Of 21 studies, 5 presented risk estimates based on different levels of exposure to shift work. Classification of exposure was based on years of shift work, with categories ranging from yearly, to 5- and 10-year exposure groups. Participants in these studies engaged in shift work from a minimum of 1 year up to >30 years. As only two studies reported an estimate for >20 or 30 years, we limited the analysis to 15 years to provide a more robust estimate. The generalized least-squared regression showed a positive non-linear dose–response relationship that was significant after the first five years of shift work, with a 7.1% (95% CI 1.05–1.10) incremental risk of CVD events for each subsequent 5-year exposure.

Table 1. Characteristics of the included studies. [CS=cohort study; CC_case–control study; CHD=coronary heart disease; CVD=cardiovascular disease; IHD=ischaemic heart disease; MI=myocardial infarction; MONICA=multinational monitoring of trends and determinants in cardiovascular disease].

Study	Study design	Follow-up	Exposure definition	Outcome	Sample size	Age [a] (SD/range)	Sex	Study population
Hublin et al, 2010 (26)	CS	1982–2003	Mainly shift-work	CHD mortality & disability	20 142	40.2 (24–60)	M&F	Twin study, Finland [c]
Natti et al, 2012 (38)	CS	1975–ongoing	Worked during the night (23:00-06:00), weekly	CVD mortality, all-cause	3095	37.0 (11.1)	M&F	National survey, Finland*
Gu et al, 2015 (16)	CS	1976–ongoing	≥3 nights/month + day/evening shifts	CVD mortality	74 862	64.6 (7.1)	F	Nurses health study, US
Ervasti et al, 2016 (27)	CC	2005–2011	Shift work without/with night shifts, and other type of shift work	CVD, mortality & disability	14 514	50.8 (7.7); 52.1 (7.4)	M&F	Municipal workers, Finland
Tüchsen et al, 2006 (33)	CS	1991–2012	2- and 3-shifts, irregular work, rotational/permanent night & evening	Circulatory disease risk	5517	36 (11)–38 (11)	M&F	Population study, Denmark*
Hermansson et al, 2015 (29)	CC	1971–1995	Shift work and variable work-hours	MI mortality after MI	1961	57.11 (5.77)	M&F	Stockholm heart study, Sweden*
Cheng et al, 2014 (41)	CC	2007–2011	Other than fixed day-shift	MI and CHD risk	966	51.5 (7.1)	M&F	Hospital cases and National survey, Taiwan [c]
Yadegarfar & McNamee, 2008 (20)	CC	1950–1998	2- and 3-shifts, any direction/system	IHD risk	1270	48.5 (13.2); 47.8 (13.4)	M	Nuclear fuel workers, UK
Yong et al, 2014 (19)	CS	1995–2009	12h-shifts (fast-forward-rotating)	IHD & circulatory disease mortality	31 143	41.2 (11.1)	M	Chemical workers, Germany,
Wang et al, 2016 (34)	CS	1984–2011	Evening/night/rotating shifts, ≥5 days/week	IHD risk/mortality	1891	51.5 (5.1), 53.5 (3.9)	M	Kuopio IHD study, Finland [c]
Fujino et al, 2006 (37)	CS	1988–2003	Fixed night or rotational shift	IHD & circulatory disease mortality	17 649	48.5 (5.9)	M	Population study, Japan
Allesøe et al, 2010 (36)	CS	1993–2008	Evening, night, rotational	IHD risk	12 116	51 (45–64)	F	Danish nurse cohort study, Denmark
Brown et al, 2009 (17)	CS	1988–2004	≥3 nights/month + day/evening shifts	Ischemic stroke	80 108	56.3 (6.9)	F	Nurses health study, US
Hermansson et al, 2007 (35)	CC	1985–2004	Shift work including variable hours	Ischemic stroke risk	834	54.7 (30–74)	M&F	Population survey MONICA, Sweden [c]
Kim et al, 2013 (28)	CC	2002–2004	Day/night shift of work time on a regular basis	Haemorrhagic stroke	2820	54.1 (11.4), 53.6 (11.6)	M&F	Population study, Taiwan [c]
Vetter et al, 2016 (18)	CS	1988–2013	≥3 nights/month + day/evening shifts	CHD risk & CHD/MI mortality	73 623	54.3 (7.1)	F	Nurses health study, US
Virkkunen et al, 2006 (30)	CS	1987–1999	2- and 3-shift work, irregular work, night shift	CHD risk	1804	45–62	M	Paper and pulp/oil workers, Finland
Virkkunen et al, 2007 (31)	CS	1988–1995/99	2- and 3-shift work, irregular work, night shift	CHD risk, pre-existing risk	1288	51.8 (45–60)	M	Paper and pulp/oil workers, Finland
Biggi et al, 2008 (40)	CS	1976–2007	Night shift, 6 days/week	CHD risk	488	44.6 (22–67)	M	Municipal cleaners, Italy
Ellingsen et al, 2007 (32)	CS [b]	1972–2003	Rotating shifts, 2 mornings-2 afternoon-2 night system	CHD risk	2562	46.1 (7.0); 49.3 (6.7)	M	Fertilizer plant workers, Middle East
Wang et al, 2015 (39)	CS	1987–2001	Evening/night/rotating shifts, ≥5 days/week	CVD markers: Arteriosclerosis	854	50.7	M	Kuopio IHD study, Finland [c]

[a] Average age at baseline or the highest mean when the study presented the population in stratified groups.
[b] Retrospective cohort study.
[c] These studies did not specify type of industry/workers.

Sensitivity analysis

Results of the first sensitivity (meta-regression) analysis are shown in table 3. The only contribution to heterogeneity was sample size, which explained only 7.7% of the variance. This analysis showed that ES were slightly higher when cohort studies, studies with a sample size <10 000, and studies with moderate risk of bias, were considered. However, none of the odds ratios in these analyses were significantly different from null, and their ES were not significantly different from the reference (index) category's estimated pooled ES (table 3).

The results of the second sensitivity analysis (meta-regression exploring the potential effects of bias in more detail) are shown in table S2 (add www.sjweh.fi/show_abstract.php?abstract_id=3700). "Exposure assessment" was considered to be the major potential source of bias because 17 studies scored as high risk on this criterion (total N=30 estimates included in the meta-analysis). The pooled ES from these studies was higher than for studies that scored low risk on this item, but the difference was not significant. One study with

Table 2. Risk of bias assessment

Study	Risk of bias per item										Overall risk of bias
	Major Domain					Minor Domain [a]					
	1	2	3	4	5	1	2	3	4	5	
Cohort studies											
Allesøe et al 2010 (36)	1	1	0	0	0	U	U	0	0	0	High
Biggi et al 2008 (40)	0	0	0	0	0	U	U	0	U	U	Low
Brown et al 2009 (17)	0	1	0	0	0	U	U	0	0	0	Moderate
Ervasti et al 2016 (27)	1	1	0	0	0	U	U	0	0	0	High
Fujino et al 2006 (37)	1	1	0	0	0	U	U	0	0	0	High
Gu et al 2015 (16)	0	1	0	0	0	U	0	0	0	0	Moderate
Hublin et al 2010 (26)	1	1	0	0	0	U	0	0	U	0	High
Natti et al 2012 (38)	1	1	0	0	0	U	0	0	0	0	High
Tüchsen et al 2006 (33)	0	1	0	0	0	U	U	0	U	0	Moderate
Vetter et al 2016 (18)	0	1	0	0	0	0	0	0	0	0	Low
Virkkunen et al 2006 (30)	0	1	0	0	0	U	U	0	0	0	Moderate
Virkkunen et al 2007 (31)	0	1	0	0	0	U	U	0	0	U	Moderate
Wang et al 2015 (39)	0	1	0	0	0	U	1	0	0	0	Moderate
Wang et al 2016 (34)	0	1	0	0	0	U	U	0	0	0	Moderate
Yong et al 2014 (19)	0	0	0	0	0	0	0	0	U	0	Low
Case-control studies											
Cheng et al 2014 (41)	1	1	0	0	1	U	0	0	0	0	High
Ellingsen et al 2007 (32)	0	0	0	0	1	U	U	0	U	U	Moderate
Hermansson et al 2007 (35)	1	1	0	0	0	U	U	0	U	U	High
Hermansson et al 2015 (29)	0	1	0	0	0	U	U	0	U	0	Moderate
Kim et al 2013 (28)	1	1	0	0	0	0	U	0	0	0	High
Yadegarfar et al 2007 (20)	0	0	0	0	0	0	0	0	0	0	Low

[a] Risk of bias due to: (1) shift work exposure definition, (2) exposure assessment, (3) reliability of assessments, (4) confounders assessment, (5) analysis methods in the study (research-specific bias), (1a) blinding of assessors, (2a) attrition, (3a) selective reporting, (4a) funding, (5a) conflict of interest. 1 = high risk, 0= low risk; U= unclear.

high attrition had a very high ES (2.50) and explained 2.5% of the heterogeneity. Overall, those studies with 1 or 2 high-risk score items had slightly higher ES, and explained 29% of the overall heterogeneity. In contrast, studies with 3 high-risk items showed the opposite effect with a smaller pooled ES (0.85). The complete sensitivity analysis of high-risk of bias items is shown in table S2. Funnel plots showed no significant publication bias (see figures S1–S4, www.sjweh.fi/show_abstract.php?abstract_id=3700).

Discussion

Principal findings

In this meta-analysis, we found that shift work was associated with 26% increased risk of CHD morbidity and about 20% increased risk of CHD and CVD mortality. Further, the risk of developing any CVD seemed to occur after the first five years of shift work, with a 7.1% increase for every five additional years of shift work. This is the first meta-analysis to show a dose–response relationship between exposure to shift work and CVD risk. Our findings contribute to the evidence

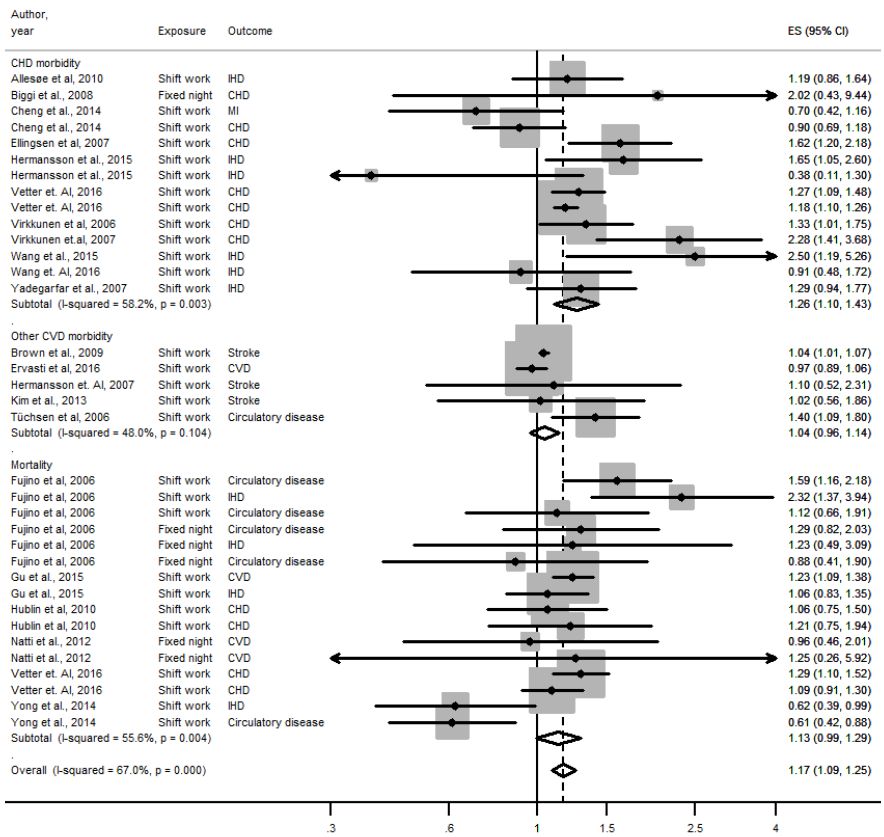

Figure 2. Meta-analysis of associations between shift work and cardiovascular disease events, grouped by CHD and other CVD morbidity, and CVD mortality (N=21 studies).

of a dose–response relationship between shift work and other health outcomes, which is limited so far to meta-analyses on cancer risk (8, 9).

Strengths and limitations

We performed an extensive literature review with clear inclusion criteria, so that we could include as many relevant studies as possible. A strength was the use of rigorous methodology to interrogate dose–response relationships (15, 21) and the use of meta-regression sensitivity analyses. Another strength was the use of a previously validated tool for rigorous assessment of risk of bias, which was used to conduct meta-regression analysis on the overall risk of bias and on each of the high-risk items (table S2). Only "attrition" seemed to explain 2.3% of the heterogeneity, but since there was only one estimate in the high-risk group, it is unlikely that one out of 35 estimates inflated our results. Although not statistically significantly different, those studies with no high risk of bias scores resulted in lower ES estimates than those with one or two high risk of bias scores. Interpretation of these sensitivity analyses is challenging, because it would appear that studies with high risk of bias on both "shift work exposure definition" and "exposure assessment" items had higher ES, which would indicate that our conclusions should be viewed with caution. However, neither of these estimates was statistically significantly higher than for the low risk estimates, and when assessed separately, neither of these items appeared to explain the heterogeneity in the overall ES estimate.

One limitation in our study may be the inclusion of only one or two estimates from studies that presented a high number of sub-group estimates, but we limited any inclusion or selection bias by providing a clear rationale for selecting estimates for inclusion. The main limitation was that studies used different terms to describe CVD outcomes, thus there might have been misclassification of the two CVD outcome groups.

Comparison with other studies

The findings concur with those of Wang et al (8), who found a slightly greater (11%, compared with 7.1% here) increased risk of colon cancer for every five years of shift work exposure. However, their analysis showed a linear relationship, based on three studies with up to five years of exposure. In another study, researchers reported a 13% increase in breast cancer risk for every 500 night shifts worked (9). This study however, used a different analysis, with cumulative risk of number of shifts worked, rather than years of exposure, and included data from more studies (N=10) than we did (N=5). Notwithstanding these differences, we observed that the risk of CVD only increased after the first five

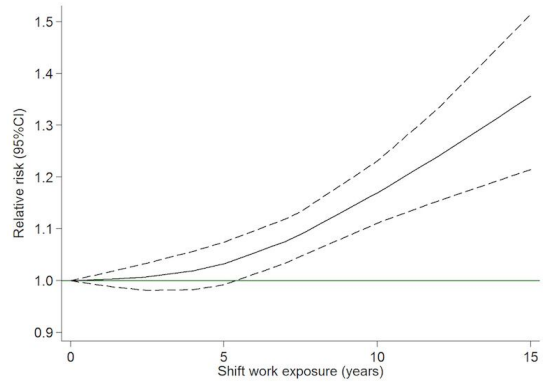

Figure 3. Dose-response relationship between years of shift work and risk of any CVD event. Relative risk was calculated with 16 estimates from N=5 cohort studies including N=13440 cases of CVD events. Dashed lines indicate 95% confidence interval.

Table 3. Analysis of potential contributing factors to the effect of shift work on cardiovascular disease events. [ES=effect size; OR=odds ratio; CI=confidence interval; CHD=coronary heart disease; CVD=cardiovascular disease].

Covariate/ sub-group	N	ES pooled (95% CI)	I^2	Meta-regression OR (95% CI)	% heterogeneity explained (R^2)
Type of outcome					
CHD morbidity	14	1.26 (1.10–1.43)	58.2	Index	-10.9
Other CVD morbidity	5	1.04 (0.96–1.14)	48.0	0.88 (0.65–1.20)	
Mortality	16	1.13 (0.99–1.29)		0.86 (0.59–1.26)	
Sex					-23.3
Both	7	1.20 (0.91–1.57)	66.8	Index	
Female	11	1.16 (1.07–1.25)	66.7	0.96 (0.71–1.30)	
Male	16	1.21 (0.99–1.48)	64.2	1.01 (0.75–1.37)	
Industry type					-23.3
Nursing	8	1.16 (1.07–1.25)	84.4	Index	
General/office	21	1.17 (1.02–1.35)	51.4	1.00 (0.75–1.34)	
Chemical/ Nuclear	6	1.16 (0.81–1.67)	74.1	0.99 (0.74–1.34)	
Design					-5.0
Cohort	28	1.18 (1.10–1.28)	70.4	Index	
Case-control	7	1.03 (0.80–1.34)	49.2	0.87 (0.66–1.15)	
Age					
Young	14	1.20 (0.97–1.49)	64.1	Index	-3.6
Old	21	1.14 (1.06–1.28)	66.8	0.95 (0.76–1.19)	
Sample size					7.7
<10 000	16	1.26 (1.06–1.50)	52.1	Index	
>10 000	19	1.13 (1.04–1.22)	70.9	0.89 (0.72–1.10)	
Risk of bias					-10.2
Low	8	1.10 (0.96–1.26)	69.6	Index	
Moderate	11	1.30 (1.12–1.51)	75.4	1.20 (0.94–1.55)	
High	16	1.11 (0.98–1.26)	50.7	1.04 (0.81–1.33)	
Overall	35	1.17 (1.09–1.25)	67.0		

years of exposure, which is in line with findings from previous cohort studies and expert reviews (42–44).

Although our outcome categorization was slightly different, our estimate for risk of CHD morbidity (ES:1.26; 95% CI 1.10–1.43) was comparable with that reported in a previous meta-analysis by Vyas et al (7) (ES: 1.24, 95% CI 1.20–1.39) for coronary events. Both studies found very similar associations between shift work and CVD-related mortality, but neither estimate quite reached statistical significance (ES: 1.14, 95% CI 0.98–1.32) in the Vyas et al study, compared with 1.13 (95% CI 0.99–1.29) (7). However, our sub-group analyses showed that the risks for CHD and CVD mortality were significantly increased among shift workers, (ES: 1.18, 95% CI 1.03–1.32 and ES: 1.22, 95% CI 1.09–1.37, respectively) while those reported by Vyas et al (7), did not reach statistical significance (ES: 1.08, 95% CI 0.97–1.21 and ES: 1.14, 95% CI 0.98–1.32, respectively). In terms of overall risk of CVD events, our results also differ from those reported by Bøggild & Knutsson (1999), who found that shift workers were at 40% increased risk of CVD (45). These differences probably reflect variations in the included studies.

The review by Vyas et al (7), included studies published from ~1970 until 2011. We only included studies published since 2006, as these tend to be of higher quality and also because our aim was to update the previous meta-analysis. Indeed, the studies that presented estimates for CHD and CVD mortality were published in recent years (2010–2016) and thus most of these (16, 18, 38) were not included by Vyas et al (7), which may explain some of the different results. Ten studies have reported on shift work and the risk of CVD since the previous meta-analysis (16, 18, 19, 27–29, 34, 38, 39, 41); these are included in our study. This could explain differences in the observed heterogeneity, with our study showing less heterogeneity for CHD events than was reported in the previous review (I^2 = 58% vs I^2= 85%).

Heterogeneity in our results was partially explained by sample size. Other factors did not explain heterogeneity, but some study characteristics showed higher ES in the sensitivity analyses. One of these was shift work definition, which is a recognized limitation in shift work research, in particular for epidemiological studies (7, 26, 42). Given the metabolic and lifestyle consequences of not following a normal sleep/wake cycle (desynchronized circadian rhythm) (2), the definition of "shift work" exposure should include the duration of exposure, shift system, and intensity. Using a consistent definition across studies (ie, rotation direction, length of shift, alternation and number of days off) could lead to a more appropriate classification of individuals in future shift work research. This would result in a more accurate estimation of risks associated with different schedules, which is of value for workforce planning and public policy.

Other considerations in this meta-analysis include the discrepancy among studies in both the direction and strength of the association between shift work and CVD risk, which was independent of risk of bias. This could be explained by the "healthy shift worker" effect, which is another limitation in this research field (19). This means that only healthy employees are selected into shift work, based on pre-employment screening, or self-selection out of shift work due to ill health (19, 46). Such bias could lead to CVD cases being underestimated in longitudinal studies, if shift workers changed to day shift or had left the workforce at follow-up because they developed CVD. Only a few studies reported strategies to control this bias, such as classifying participants at follow-up based on whether they maintained the same shift from baseline or not (26).

Future research

A potential approach to limiting the "healthy shift worker" bias in future studies would be to give more consideration to other factors, such as lifestyle behaviors. Research has shown that physical inactivity, smoking, obesity and poor diet are more prevalent in shift workers (4, 5). However, these potential mediators of the relationship between shift work and healthy outcomes are rarely considered in shift work research, which tends to focus on sleep patterns as the underlying mechanism of chronic disease development (47). Accurate reporting of lifestyle behaviors could also shed light on any "healthy" or "unhealthy" bias when assessing the risk of cardiovascular disease in shift workers (25). Thus, it is important that future studies measure, report and include these factors in the adjusted models of risk estimates, to enable better interpretation of results.

Concluding remarks

Our data indicate that shift workers have higher risk of CVD morbidity and mortality than non-shift workers, with a 7.1% incremental risk for every five years of shift work exposure after the first five years. Future research should provide a clear and consistent definition of shift work in order to better understand whether CVD risk is associated with any specific shift work pattern. As many industries, including the healthcare sector, depend on shift work to meet production and service demands, workplace health promotion initiatives could help limit shift workers' CVD risk.

Conflict of interest and funding

The authors declare no conflict of interest

References

1. Boivin DB, Boudreau P. Impacts of shift work on sleep and circadian rhythms. Pathol Biol (Paris). 2014;62(5):292–301. https://doi.org/10.1016/j.patbio.2014.08.001.
2. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A. 2009;106(11):4453–8. https://doi.org/10.1073/pnas.0808180106.
3. Puttonen S, Härmä M, Hublin C. Shift work and cardiovascular disease—pathways from circadian stress to morbidity. Scand J Work Environ Health. 2010:96–108. https://doi.org/10.5271/sjweh.2894.
4. Bekkers MB, Koppes LL, Rodenburg W, van Steeg H, Proper KI. Relationship of night and shift work with weight change and lifestyle behaviors. J Occup Environ Med. 2015;57(4):e37–44. https://doi.org/10.1097/JOM.0000000000000426.
5. Esquirol Y, Perret B, Ruidavets JB, Marquie JC, Dienne E, Niezborala M, et al. Shift work and cardiovascular risk factors: new knowledge from the past decade. Arch Cardiovasc Dis. 2011;104(12):636–68. https://doi.org/10.1016/j.acvd.2011.09.004.
6. Wang XS, Armstrong ME, Cairns BJ, Key TJ, Travis RC. Shift work and chronic disease: the epidemiological evidence. Occup Med (Lond). 2011;61(2):78–89. https://doi.org/10.1093/occmed/kqr001.
7. Vyas MV, Garg AX, Iansavichus AV, Costella J, Donner A, Laugsand LE, et al. Shift work and vascular events: systematic review and meta-analysis. BMJ. 2012;345(7871):e4800. https://doi.org/10.1136/bmj.e4800.
8. Wang X, Ji A, Zhu Y, Liang Z, Wu J, Li S, et al. A meta-analysis including dose–response relationship between night shift work and the risk of colorectal cancer. Oncotarget. 2015;6(28):25046–60. https://doi.org/10.18632/oncotarget.4502.
9. Wang F, Yeung KL, Chan WC, Kwok CC, Leung SL, Wu C, et al. A meta-analysis on dose–response relationship between night shift work and the risk of breast cancer. Ann Oncol. 2013;24(11):2724–32. https://doi.org/10.1093/annonc/mdt283.
10. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–12. https://doi.org/10.1001/jama.283.15.2008.
11. WHO. Cardiovascular diseases (CVDs) fact sheet. Geneva: World Health Organization; 2015.
12. Proper KI, van de Langenberg D, Rodenburg W, Vermeulen RC, van der Beek AJ, van Steeg H, et al. The relationship between shift work and metabolic risk factors: A systematic review of longitudinal studies. Am J Prev Med. 2016;50(5):e147–e57. https://doi.org/10.1016/j.amepre.2015.11.013.
13. Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of shift-work, painting, and fire-fighting. Elsevier; 2007.
14. Ijaz S, Verbeek J, Seidler A, Lindbohm M-L, Ojajärvi A, Orsini N, et al. Night-shift work and breast cancer – a systematic review and meta-analysis. Scand J Work Environ Health. 2013(5):431–47. https://doi.org/10.5271/sjweh.3371.
15. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose–response data, with applications to meta-analysis. Am J Epidemiol. 1992;135(11):1301–9. https://doi.org/10.1093/oxfordjournals.aje.a116237.
16. Gu F, Han J, Laden F, Pan A, Caporaso NE, Stampfer MJ, et al. Total and cause-specific mortality of U.S. nurses working rotating night shifts. Am J Prev Med. 2015;48(3):241–52. https://doi.org/10.1016/j.amepre.2014.10.018.
17. Brown DL, Feskanich D, Sanchez BN, Rexrode KM, Schernhammer ES, Lisabeth LD. Rotating night shift work and the risk of ischemic stroke. Am J Epidemiol. 2009;169(11):1370–7. https://doi.org/10.1093/aje/kwp056.
18. Vetter C, Devore EE, Wegrzyn LR, Massa J, Speizer FE, Kawachi I, et al. Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease Among Women. JAMA. 2016;315(16):1726–34. https://doi.org/10.1001/jama.2016.4454.
19. Yong M, Nasterlack M, Germann C, Lang S, Oberlinner C. Shift work and risk of non-cancer mortality in a cohort of German male chemical workers. Int Arch Occup Environ Health. 2014;87(7):763–73. https://doi.org/10.1007/s00420-013-0922-5.
20. Yadegarfar G, McNamee R. Shift work, confounding and death from ischaemic heart disease. Occup Environ Med. 2008;65(3):158–63. https://doi.org/10.1136/oem.2006.030627.
21. Royston P. A strategy for modelling the effect of a continuous covariate in medicine and epidemiology. Stat Med. 2000;19(14):1831–47. https://doi.org/10.1002/1097-0258(20000730)19:14<1831::AID-SIM502>3.0.CO;2-1.
22. Bagnardi V, Zambon A, Quatto P, Corrao G. Flexible meta-regression functions for modeling aggregate dose–response data, with an application to alcohol and mortality. Am J Epidemiol. 2004;159(11):1077–86. https://doi.org/10.1093/aje/kwh142.
23. Haupt CM, Alte D, Dörr M, Robinson DM, Felix SB, John U, et al. The relation of exposure to shift work with atherosclerosis and myocardial infarction in a general population. Atherosclerosis. 2008;201(1):205–11. https://doi.org/10.1016/j.atherosclerosis.2007.12.059.
24. Jankowiak S, Backe E, Liebers F, Schulz A, Hegewald J, Garthus-Niegel S, et al. Current and cumulative night shift work and subclinical atherosclerosis: results of the Gutenberg Health Study. Int Arch Occup Environ Health. 2016;89(8):1169–82. https://doi.org/10.1007/s00420-016-1150-6.
25. Jacobsen HB, Reme SE, Sembajwe G, Hopcia K, Stiles TC, Sorensen G, et al. Work stress, sleep deficiency, and predicted 10-year cardiometabolic risk in a female patient care worker population. Am J Ind Med. 2014;57(8):940–9. https://doi.

org/10.1002/ajim.22340.

26. Hublin C, Partinen M, Koskenvuo K, Silventoinen K, Koskenvuo M, Kaprio J. Shift-work and cardiovascular disease: a population-based 22-year follow-up study. Eur J Epidemiol. 2010;25(5):315–23. https://doi.org/10.1007/s10654-010-9439-3.

27. Ervasti J, Kivimaki M, Pentti J, Salo P, Oksanen T, Vahtera J, et al. Health- and work-related predictors of work disability among employees with a cardiometabolic disease--A cohort study. J Psychosom Res. 2016;82:41–7. https://doi.org/10.1016/j.jpsychores.2016.01.010.

28. Kim BJ, Lee SH, Ryu WS, Kim CK, Chung JW, Kim D, et al. Excessive work and risk of haemorrhagic stroke: a nationwide case-control study. Int J Stroke. 2013;8 Suppl A100:56–61.

29. Hermansson J, Gillander Gadin K, Karlsson B, Reuterwall C, Hallqvist J, Knutsson A. Case fatality of myocardial infarction among shift workers. Int Arch Occup Environ Health. 2015;88(5):599–605. https://doi.org/10.1007/s00420-014-0984-z.

30. Virkkunen H, Harma M, Kauppinen T, Tenkanen L. The triad of shift work, occupational noise, and physical workload and risk of coronary heart disease. Occup Environ Med. 2006;63(6):378–86. https://doi.org/10.1136/oem.2005.022558.

31. Virkkunen H, Harma M, Kauppinen T, Tenkanen L. Shift work, occupational noise and physical workload with ensuing development of blood pressure and their joint effect on the risk of coronary heart disease. Scand J Work Environ Health. 2007;33(6):425–34. https://doi.org/10.5271/sjweh.1170.

32. Ellingsen T, Bener A, Gehani AA. Study of shift work and risk of coronary events. J R Soc Promot Health. 2007;127(6):265–7. https://doi.org/10.1177/1466424007083702.

33. Tuchsen F, Hannerz H, Burr H. A 12 year prospective study of circulatory disease among Danish shift workers. Occup Environ Med. 2006;63(7):451–5. https://doi.org/10.1136/oem.2006.026716.

34. Wang A, Arah OA, Kauhanen J, Krause N. Shift work and 20-year incidence of acute myocardial infarction: results from the Kuopio Ischemic Heart Disease Risk Factor Study. Occup Environ Med. 2016;73(9):588–94. https://doi.org/10.1136/oemed-2015-103245.

35. Hermansson J, Gillander Gadin K, Karlsson B, Lindahl B, Stegmayr B, Knutsson A. Ischemic stroke and shift work. Scand J Work Environ Health. 2007;33(6):435–9. https://doi.org/10.5271/sjweh.1165.

36. Allesoe K, Hundrup YA, Thomsen JF, Osler M. Psychosocial work environment and risk of ischaemic heart disease in women: the Danish Nurse Cohort Study. Occup Environ Med. 2010;67(5):318–22. https://doi.org/10.1136/oem.2008.043091.

37. Fujino Y, Iso H, Tamakoshi A, Inaba Y, Koizumi A, Kubo T, et al. A prospective cohort study of shift work and risk of ischemic heart disease in Japanese male workers. Am J Epidemiol. 2006;164(2):128–35. https://doi.org/10.1093/aje/kwj185.

38. Natti J, Anttila T, Oinas T, Mustosmaki A. Night work and mortality: prospective study among Finnish employees over the time span 1984 to 2008. Chronobiol Int. 2012;29(5):601–9. https://doi.org/10.3109/07420528.2012.675262.

39. Wang A, Arah OA, Kauhanen J, Krause N. Work schedules and 11-year progression of carotid atherosclerosis in middle-aged Finnish men. Am J Ind Med. 2015;58(1):1–13. https://doi.org/10.1002/ajim.22388.

40. Biggi N, Consonni D, Galluzzo V, Sogliani M, Costa G. Metabolic syndrome in permanent night workers. Chronobiol Int. 2008;25(2):443–54. https://doi.org/10.1080/07420520802114193.

41. Cheng Y, Du CL, Hwang JJ, Chen IS, Chen MF, Su TC. Working hours, sleep duration and the risk of acute coronary heart disease: a case-control study of middle-aged men in Taiwan. Int J Cardiol. 2014;171(3):419–22. https://doi.org/10.1016/j.ijcard.2013.12.035.

42. Knutsson A. Methodological aspects of shift-work research. Chronobiol Int. 2004;21(6):1037–47. https://doi.org/10.1081/CBI-200038525.

43. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Speizer FE, et al. Prospective study of shift work and risk of coronary heart disease in women. Circulation. 1995;92(11):3178–82. https://doi.org/10.1161/01.CIR.92.11.3178.

44. Knutsson A, Akerstedt T, Jonsson BG, Orth-Gomer K. Increased risk of ischaemic heart disease in shift workers. Lancet. 1986;2(8498):89–92. https://doi.org/10.1016/S0140-6736(86)91619-3.

45. Bøggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. Scand J Work Environ Health. 1999:85–99. https://doi.org/10.5271/sjweh.410.

46. Oberlinner C, Ott MG, Nasterlack M, Yong M, Messerer P, Zober A, et al. Medicai program for shift workers-impacts on chronic disease and mortality outcomes. Scand J Work Environ Health. 2009:309–18. https://doi.org/10.5271/sjweh.1332.

47. van Mark A, Weiler SW, Schroder M, Otto A, Jauch-Chara K, Groneberg DA, et al. The impact of shift work induced chronic circadian disruption on IL-6 and TNF-alpha immune responses. J Occup Med Toxicol. 2010;5(1):18. https://doi.org/10.1186/1745-6673-5-18.

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