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Review Article

# Associations of shift work and night work with risk of all-cause, cardiovascular and cancer mortality: a meta-analysis of cohort studies

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A R T I C L E I N F O

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A B S T R A C T

*Background:* Epidemiological studies on the relationship of shift work or night work with risk of total and cause-specific mortality have given conflicting results. We aimed at conducting a meta-analysis to summarize the evidence from cohort studies.

*Methods:* Embase, PubMed, Web of Science and Scopus databases were searched for eligible studies up to Mar 2021. Cohort studies evaluating the associations of shift work or night work with risk of all-cause, cardiovascular or cancer mortality were reviewed. Study-specific risk estimates were pooled by fixed-effect models when the heterogeneity was not detected; otherwise, random-effect models were employed.

*Results:* We identified seventeen eligible articles (sixteen cohorts). A total of 958,674 cohort participants were included, with 38,413 total deaths, 24,713 cardiovascular deaths and 10,219 cancer deaths during follow-up. According to the Newcastle–Ottawa Scale, fifteen studies were considered as relatively high quality with low risk of bias. Compared with regular daytime workers, the pooled relative risks for all-cause, cardiovascular and cancer mortality were 1.02 (95% CI: 0.99, 1.06), 1.18 (95% CI: 0.94, 1.47) and 1.05 (95% CI: 0.83, 1.34) for those ever exposing to shift work, respectively. Compared with daytime workers or those never exposing to night work, the pooled relative risks for all-cause, cardiovascular and cancer mortality were 1.06 (95% CI: 1.03, 1.08), 1.15 (95% CI: 1.03, 1.29) and 1.04 (95% CI: 1.00, 1.08) for those ever exposing to night work, respectively. Moderate to high level of heterogeneity across the studies was detected. Publication bias was not detected.

*Conclusion:* Night work may be associated with higher risk of all-cause, cardiovascular and cancer mortality, suggesting that night workers compared with daytime workers may be at higher risk of death, especially due to cardiovascular disease.



## 1. Introduction

Shift work, usually defined as all work that is not scheduled during the daytime, is a common form of work scheduling worldwide [1]. It is reported that the majority of the working population is involved in irregular working schedules, such as night-shift, evening-shift or rotating-shift work [1]. Shift work can influence workers' health, hamper family and social life, and subsequently lead to high social cost and burden [1,2]. Previous studies indicated that shift work is a risk factor for many health disorders, such as gastrointestinal diseases, metabolic disorders, cardiovascular diseases (CVD) and cancer [1,3,4].

An increasing amount of epidemiological studies showed that shift work or night work may be associated with the risk of death from CVD, major cancers and other causes [5–10]. For example, in a prospective cohort study of registered U.S. nurses, women working rotating night shifts for >5 years was associated with a modest increase in all-cause and CVD mortality; those working >15 years of rotating night shift work may be at higher risk of lung cancer mortality [7]. In line with these findings from Western population, a prospective study of Japanese male workers also demonstrated a significant association between rotating-shift work and higher risk of death due to ischemic heart disease (IHD) [9]. However, there is still a large number of cohort studies which did not observe any

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significant associations of shift work with risk of all-cause and cause-specific mortality [11–15]. Two earlier meta-analyses have tried to address this inconsistency. However, due to limited number of included cohort studies, no clear evidence was found on the association of shift work with all-cause mortality. For the risk of death due to CVD-related events, a previous meta-analysis of four prospective cohort studies suggested increased risks of mortality for shift workers due to myocardial infarction (MI), IHD and coronary heart disease (CHD) [10]. Of note, risk of total CVD mortality has not been evaluated in previous meta-analysis.

Understanding the relation between shift work or night work and mortality is important for development of occupational health guidelines to protect workers' health and well-being. Although several meta-analyses have been reported, relationship between shift work and risk of death is still unclear and inconclusive. Since CVD and cancer are two major causes of death worldwide, we aim at conducting a meta-analysis by summarizing the most up-to-date evidence to systematically evaluate the association between shift work or night work and risk of total deaths, as well as deaths due to CVD and cancer.

## 2. Methods

This study was performed in adherence to PRISMA guidance (Supplementary Table S1) [16]. This is a meta-analysis based on study-level data, and no patient- or individual-level data were collected or analyzed; thus, informed consent was not required.

There are different definitions on shift work and night work in previous literatures (Supplementary Table S2). Based on the definition from International Agency for Research on Cancer, shift work is generally defined as all work that is not scheduled during the daytime (eg, outside the regular working hours between 7–8 am and 5–6 pm). In this meta-analysis, we compared the risk of death in population ever exposing to any types of shift work with those never exposing to shift work or regular daytime workers. Besides, it is general regarded night work as one of the major types of shift work. We also compared the risk of death in population ever exposing to night work with those never exposing to night work or daytime workers.

### 2.1. Literature search and study selection

Two researchers independently conducted the literature search and study selection. Discrepancies were addressed by discussion. A systematic search was conducted up to 31 March 2021 of online databases including Embase, PubMed, Web of Science and Scopus without language limitation. We searched Google Scholar for grey literature. To avoid missing any potential studies, reference lists of relevant studies/reviews were also checked. The details of database search strategies were presented in Supplementary Table S3.

To identify eligible studies, we used the following inclusion criteria: (1) cohort design; (2) studies should report any types of shift work (such as regular evening work, regular night work, regular morning work, 2-shift work, 3-shift work, or other shift schedules) as the exposure in comparison with regular daytime work as the non-exposure; or report any types of night work (rotating or permanent night shifts) as the exposure in comparison with never night work or daytime work (with or without shift) as the non-exposure; (3) reporting deaths from all-cause, total CVD events, or total cancers as the outcome of interest; (5) reporting relative risk (RR), risk ratio, rate ratio, hazard ratio, odds ratio with the corresponding 95% confidence interval (CI) as the measure of association. When two or more studies covered the same study population, we selected the most informative study, or most recent study, or extracted information from both studies as appropriate. We excluded editorial, letters, comments, abstracts, posters, meta-analysis and reviews. We also excluded studies with insufficient information, eg, studies only reporting data on specific cancer subtypes or CVD subtypes as the outcome.

### 2.2. Data extraction

For each eligible study, the following information were extracted: the first author, publication year, study design, study location, study population, size of cohort, age at baseline, sex, exposure definition, exposure assessment, outcomes, outcome ascertainment, number of deaths, follow-up time, risk estimates, and confounder adjustment.

### 2.3. Study quality assessment

The 9-star Newcastle–Ottawa Scale [17] was used to evaluate the quality of eligible cohort studies. A cohort study was judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest. “High” quality choices were assigned with a maximum of two stars for items in “comparability” category, and with one star for other numbered items. For example, for the item of “ascertainment of exposure”, a study with exposure information collected by questionnaire or personnel work history was assigned one star, whereas a study collected exposure information by job exposure matrixes derived from job titles only did not assigned a star. Based on the criteria from previous meta-analyses [18,19], a study assessed with $\geq$7 stars could be considered as high quality study.

### 2.4. Statistical analysis

To assess the associations of shift work or night work with risk of all-cause, CVD and cancer mortality, RR were used as the risk estimate in the meta-analysis. We pooled the study-specific RRs using fixed-effect models when statistical heterogeneity was not detected; otherwise, the random-effect models were employed [20]. Heterogeneity was evaluated by using the $I^2$ statistic; statistical heterogeneity was indicated if $I^2$ statistic was greater than 50% [21]. To evaluate the influence of individual studies on the overall estimates, sensitivity analyses were conducted by excluding each study in turn and repeating the meta-analyses with the remaining studies. Publication bias was examined by visual inspection of the funnel plots, as well as formal statistical assessment by Egger's linear regression test and Begg's rank correlation test [22,23]. Statistical significance was considered as P value of less than 0.05. Statistical analyses were conducted using Stata software (version 14.0).

## 3. Results

### 3.1. Literature search

The literature search identified 918 records from Embase, PubMed, Web of Science and Scopus databases. After checking the titles and abstracts, we identified 31 highly relevant studies for further full-text review. We excluded 14 studies after reviewing these articles because of (i) no information on shift work or night work as the exposure ($n = 2$) [24,25]; (ii) only reporting CVD subtypes, such as IHD, MI, CHD or stroke-related mortality, as the outcome of interest ($n = 5$) [26–30]; (iii) only reporting information on death from other causes (eg injury) ($n = 1$) [14]; (iv) lack of risk estimate and/or the corresponding 95% CI ($n = 1$) [31]; (v) reappraising previous published data or reporting same study population as previous study ($n = 2$) [13,32]; (vi) editorial/posters/

conference abstracts without full-text available ($n$ = 3) [33–35] Since two articles [36,37] reported different outcomes in same study population, we included both articles in the review. Finally, we included 17 eligible articles (16 cohorts) [5–9,11,12,15,36–44] in the meta-analysis (Fig. 1).

### 3.2. Characteristics of included studies

As shown in Table 1, a total of 958,674 cohort participants were included in the 17 eligible articles (16 cohorts). Eight cohorts included participants who could be representative of the general working population; eight cohorts (nine articles) included participants derived from a specific group of working population, eg, nurse, chemical workers etc. The majority of cohort studies was conducted in Western countries, including European countries (11 cohorts) and the US (2 cohorts); three studies were conducted in Asia countries, including China (1 cohort) and Japan (2 cohorts). Exposure information were collected and assessed by structured/unstructured questionaries, personnel work histories, or company files etc. Information on death causes was ascertained from a variety of data sources such as medical record and death registries. Nine cohorts reported an average follow-up of more than 10 years. During the follow-up, there were 38,413, 24,713 and 10,219 deaths due to all-causes, CVD and cancer, respectively. Most of the included studies reported risk estimates adjusted for the most potential confounders such as age, sex and smoking, etc. According to the Newcastle–Ottawa Scale, fifteen articles with fourteen cohort studies were considered as relatively high quality with low risk of bias (Supplementary Table S4).

### 3.3. Shift work and all-cause mortality

Ten studies reported the association between shift work and risk of all-cause mortality. Two studies reported statistically significant higher risk of total death for shift workers compared with the regular daytime workers; other studies did not detect any significant associations. The study-specific RRs ranged from 0.90 (95% CI: 0.80, 1.10) in Bøggild et al., 1999 study [15] to 1.47 (95% CI: 1.01, 2.13) in Nätti et al., 2012 study [8]. Meta-analysis of these ten studies showed a pooled RR of 1.02 (95% CI: 0.99, 1.06) with moderate heterogeneity ($I^2 = 46.9\%$, $P_{heterogeneity} = 0.049$) (Fig. 2). The pooled RRs were 1.00 (95% CI: 0.95, 1.06) for male workers and 1.03 (95% CI: 0.98, 1.08) for female workers. The risk was similar for general working population (pooled RR = 1.03; 95% CI: 0.96, 1.10) with specific groups of working population (pooled RR = 1.03; 95% CI: 0.94, 1.13). When stratified by study location, the pooled RRs were 1.03 (95% CI: 0.97, 1.10) and 1.01 (95% CI: 0.88, 1.15) for studies conducted in European and Asian countries, respectively. Eight studies reported the association between night work and all-cause mortality. Compared with daytime workers or those never exposing to night work, the pooled RR for all-cause mortality was

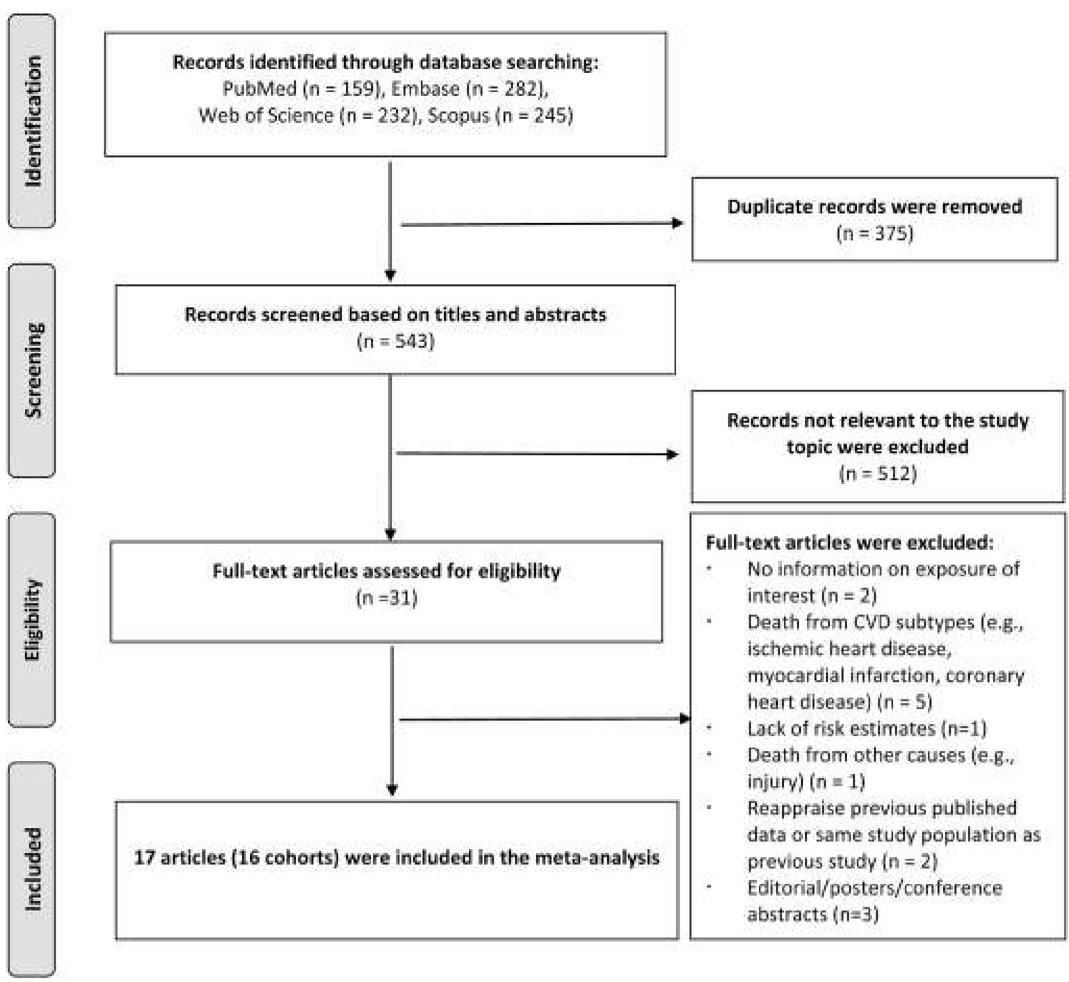


**Fig. 1.** Flow diagram of study selection.

**Table 1**
Characteristics of studies included in the meta-analysis.

| Study | Country | Cohort size/ study population | Age | Sex | Exposure vs non-exposure | Exposure assessment | Outcomes | Outcome assessment | Follow-up | Number of deaths | Confounders |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Eriksson et al., 2021 | Sweden | 4496 pulp and paper mills workers | <85 years | Female | Shift work (including night or excluding) vs daytime work without shift | Job exposure matrix | Total mortality, coronary heart disease mortality, myocardial infarction mortality, cerebrovascular disease mortality | Death registry | 167,262 person-years of follow-up | 1191 total deaths, 228 coronary heart disease deaths, 114 myocardial infarction deaths, 116 cerebrovascular disease deaths | Age, calendar year |
| Åkerstedt et al., 2020 | Sweden | 42,731; general population | 41–99 years | Both | Night work (rotating or permanent night shifts) vs never night work | Questionnaire | Total mortality, CVD mortality, cancer mortality | Death registry | 18 years of follow-up | 9494 total deaths, 3736 CVD deaths, 2983 cancer deaths | Age, sex, education, coffee consumption, smoking, body mass index, severity of disease at baseline, white/blue-collar occupational group, alcohol consumption and leisure-time physical activity |
| Hannerz et al., 2019 | Denmark | 159,933; general population | 15–74 years | Both | Night work (rotating or permanent night shifts) vs never night work | Structured questionnaire; in-person interview | Total mortality | Central person register | Average follow-up of 7.7 years | 3374 total deaths | Age, sex, socioeconomic status, calendar time, weekly working hours and time passed since the start of follow-up |
| Jørgensen et al., 2017 | Denmark | 18,015 nurses | >44 years | Female | Shift work (including and excluding night) vs daytime work without shift | Self-reported, questionnaire | Total mortality, CVD mortality, cancer mortality, ischemic heart disease, hypertension, stroke and other CVD mortality | Danish death register | Mean follow-up was 17.6 years (316,644 person-years) | 1616 total deaths, 217 CVD deaths, 945 cancer deaths | Age, smoking, pack-years, physical activity, body mass index, alcohol consumption, diet (vegetables, fruit and fatty meat consumption), pre-existing diseases (hypertension, diabetes and myocardial infarction), self-reported health, stressful work environment, marital status, female reproductive factors (birth, use of hormone therapy and oral contraceptives). |
| Barger et al., 2017 | US | 13,026 patients after an acute coronary syndrome | Median age of 64 years | Both | Night work (rotating or permanent night shifts) vs never night work | Questionnaire interview | Total mortality, | All deaths were adjudicated by a clinical events committee | Median follow-up was 2.5 years | 663 total deaths, 442 CVD deaths | Age, sex, current smoker, race, region, body mass index, hypertension, hyperlipidemia, diabetes mellitus, past myocardial infarction, past percutaneous coronary intervention, index diagnosis, days from qualifying event, catheterization for qualifying event, baseline low-density lipoprotein cholesterol, Lp-PLA2 activity, baseline estimated glomerular filtration rate <60 mL/min per 1.73 $m^2$, and randomized treatment arm. |
| Bai et al., 2016 | China | 25,377 motor corporation workers | Mean age: 62.6 years | Both | Night work (rotating or permanent night shifts) vs never night work | Questionnaire interview | Cancer mortality | Medical records and death certificates | Average follow-up of 4.5 years; 114,162 person-years | 379 cancer deaths | Age, body mass index, family history of cancer, alcohol drinking and smoking status, and gender |
| Gu et al., 2015 | US | 74,862 nurses | 30–55 years | Female | Night work (rotating or permanent night shifts) vs never night work | Mailed questionnaire | Total mortality, CVD mortality, cancer mortality, ischemic heart disease, cerebrovascular and other CVD mortality | Reports from next of kin and via postal authorities. National death index; physician review based on medical records and death certificates | 22 years of follow-up (1.5 million person-years) | 14,181 total deaths, 3062 CVD deaths, 5413 cancer deaths | Age, alcohol consumption, physical exercise, multivitamin use, menopausal status and postmenopausal hormone use, physical exam in the past 2 years, healthy eating score, smoking status, pack-years, body mass index, and husband's education |

(*continued on next page*)

**Table 1** (*continued* )

| Study | Country | Cohort size/ study population | Age | Sex | Exposure vs non-exposure | Exposure assessment | Outcomes | Outcome assessment | Follow-up | Number of deaths | Confounders |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Yong et al., 2014 (a) | Germany | 31,143 chemical workers | Mean age: 41 years | Male | Shift work (including night) vs daytime work without shift & Night work (rotating night shifts) vs never night work | Work histories | Total mortality, cancer mortality | Personnel records for active employees and death certificates | During 10 years of follow-up | 1062 total deaths, 404 cancer deaths | Age |
| Yong et al., 2014 (b) | Germany | 31,143 chemical workers | Mean age: 41 years | Male | Shift work (including night) vs daytime work without shift & Night work (rotating night shifts) vs never night work | Work histories | Non-cancer mortality, CVD mortality, ischemic heart disease mortality | Personnel records for active employees and death certificates | During 10 years of follow-up | 365 non-cancer deaths, 150 CVD deaths, 90 ischemic heart disease deaths | Age |
| Nätti et al., 2012 | Finland | 3095; general population | Mean age of 35–37 years | Both | Shift work (including night) vs daytime work without shift & Night work (rotating or permanent night shifts) vs never night work | Face-to-face interview, standard questionnaire | Total mortality, cancer mortality | Statistics Finland register | 1984–2008 | 326 total deaths | All-cause mortality: adjusted final model including age, family situation (among men), longstanding illness, and smoking status. Cancer mortality: adjusted final model including age, longstanding illness (among men), and smoking status |
| Fujino et al., 2006 | Japan | 17,649; general population | 40–59 years | Male | Shift work (including night) vs daytime work without shift & Night work (rotating or permanent night shifts) vs never night work | Self-administered questionnaire | Total mortality, CVD mortality, ischemic heart disease mortality, cerebrovascular disease mortality | Regional research centers and death certificates | 233,869 person-years of follow-up | 1363 deaths; 304 deaths fromcirculatory system disease | Age, smoking, alcohol consumption, educational level, perceived stress, past medical history, body mass index, hours of walking, hours of exercise, and job type |
| Karlsson et al., 2005 | Sweden | 5442 pulp and paper workers | 10–60 years | Male | Shift work (including night) vs daytime work without shift & Night work (rotating night shifts) vs never night work | The company files | Total mortality | National cause of death register | Mean follow-up of 30 years | 1850 deaths | Age |
| Akerstedt et al., 2004 | Sweden | 22,411; general population | 25–64 years | Both | Shift work (including night or excluding) vs daytime work without shift | Face-to-face interviews | Total mortality | Swedish cause of death register | Mean follow-up of 11.8 years | 864 deaths | Age, stress, physically strenuous work, smoking. Long-term disease was included as a stratum in the models |
| Virtanen et al., 2002 | Finland | 507,000; general population | 25–64 years | Male | Shift work (including or excluding night) vs daytime work without shift | Job exposure matrix | CVD mortality, cerebrovascular disease mortality | National register | Over 14 years follow-up | 16344 CVD deaths | Age, marital status, period, socioeconomic status, job exposure variables |
| Bøggild et al., 1999 | Denmark | 5249; general population | 40–59 years | Male | Shift work (including or excluding night) vs daytime work without shift | Questionnaire, face-to-face interview | Total mortality, ischemic heart disease mortality | Danish central population register, hospital discharge registers | 22 years of follow-up | 1679 deaths | Age, social class, sleep, tobacco, age, weight, height, fitness value |
| Tarumi; 1997 | Japan | 19,642 workers from the Japanese steel industry | 40–60 years | Male | Shift work (including or excluding night) vs daytime work without shift | Annual personnel reports. | Total mortality, stroke/ischemic heart disease mortality, cancer mortality | Company's private death certificates the annual personnel reports and the annual health examination reports of the employees | 3.9 years; 76,761.7 person-years of follow-up | 172 total deaths, 95 cancer deaths; 36 stroke/ischemic heart disease deaths | Age |
| Taylor et al., 1972 | UK | 8603; general population | ≥35 years | Male | Shift work (including or excluding night) vs daytime work without shift | Questionnaire | Total mortality | National death register | 13-year of follow-up | 1578 deaths | Age |

CVD, cardiovascular disease.

1.06 (95% CI: 1.03, 1.08; $I^2 = 0\%$, $P_{heterogeneity} = 0.512$) for those ever exposing to night work.

Sensitivity analysis showed that exclusion of single study from the analysis did not appreciably alter the pooled risk estimates (Supplementary Figure S1). No publication bias was detected based on Begg's test ($P = 0.858$) and Egger's test ($P = 0.550$), as well as visual inspection of the funnel plot (Supplementary Figure S2).

### 3.4. Shift work and CVD mortality

Four studies reported the association between shift work and risk of CVD mortality. Two studies reported statistically significant higher risk of CVD mortality for shift workers compared with the regular daytime workers; two studies did not detect any significant associations. The study-specific RRs ranged from 0.90 (95% CI: 0.66, 1.22) in Yong et al., 2014 study (b) [37] to 1.49 (95% CI: 1.15, 1.92) in Fujino et al., 2006 study [9]. Meta-analysis of these four studies showed a pooled RR of 1.18 (95% CI: 0.94, 1.47) with high heterogeneity across the studies ($I^2 = 81.3\%$, $P_{heterogeneity} = 0.001$) (Fig. 3). The risk was similar for general working population (pooled RR = 1.14; 95% CI: 0.93, 1.79) with specific groups of working population (pooled RR = 1.21; 95% CI: 0.83, 1.74). Four studies reported the association between night work and risk of CVD mortality. Compared with daytime workers or those never exposing to night work, the pooled RR for CVD mortality was 1.15 (95% CI: 1.03, 1.29; $I^2 = 58.8\%$, $P_{heterogeneity} = 0.063$) for those ever exposing to night work.

Sensitivity analysis showed that exclusion of single study from the analysis did not appreciably alter the pooled risk estimates (Supplementary Figure S3). No publication bias was detected based on Begg's test ($P = 0.734$) and Egger's test ($P = 0.353$), as well as visual inspection of the funnel plot (Supplementary Figure S4).

### 3.5. Shift work and cancer mortality

Four studies reported the association between shift work and risk of cancer mortality. One study reported statistically significant higher risk of cancer mortality for shift workers compared with the regular daytime workers, other studies did not detect any significant associations. The study-specific RRs ranged from 0.73 (95% CI: 0.39, 1.39) in Tarumi 1997 study [44] to 2.21 (95% CI: 1.23, 3.98) in Nätti et al., 2012 study [8]. Meta-analysis of these four studies showed a pooled RR of 1.05 (95% CI: 0.83, 1.34) with moderate heterogeneity across the studies was detected ($I^2 = 63.7\%$, $P_{heterogeneity} = 0.041$) (Fig. 4). Five studies reported the association between night work and risk of cancer mortality. Compared with daytime workers or those never exposing to night work, the pooled RR for cancer mortality was 1.04 (95% CI: 1.00, 1.08; $I^2 = 44.5\%$, $P_{heterogeneity} = 0.125$) for those ever exposing to night work.

Sensitivity analysis showed that exclusion of single study from the analysis did not appreciably alter the pooled risk estimates (Supplementary Figure S5). No publication bias was detected based on Begg's test ($P = 0.734$) and Egger's test ($P = 0.725$), as well as visual inspection of the funnel plot (Supplementary Figure S6).

## 4. Discussion

This meta-analysis of cohort studies suggests that night work may be associated with higher risk of all-cause mortality, suggesting that workers ever exposing to night work, compared with those who never exposed to night work, may have higher risk of death, especially due to CVD. Meta-analysis results also indicate evidence of an association between night work and risk of cancer mortality. These findings add to prior evidence of a potentially detrimental effect of night work on health and longevity.

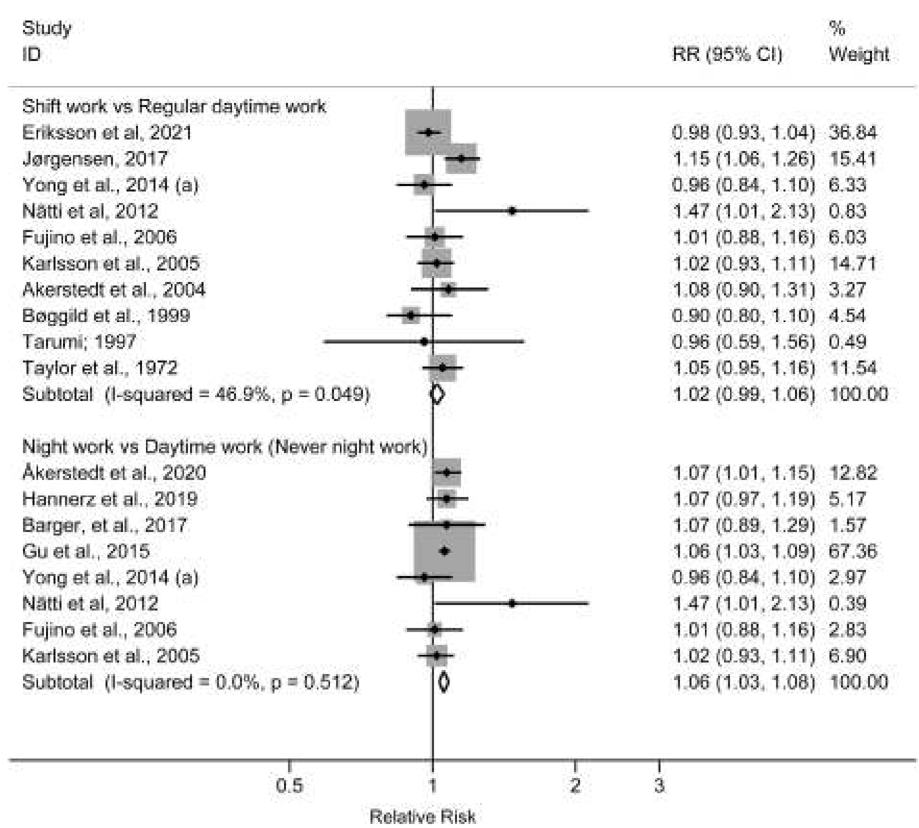


**Fig. 2.** Forest plot for association of shift work and night work with risk of all-cause mortality.

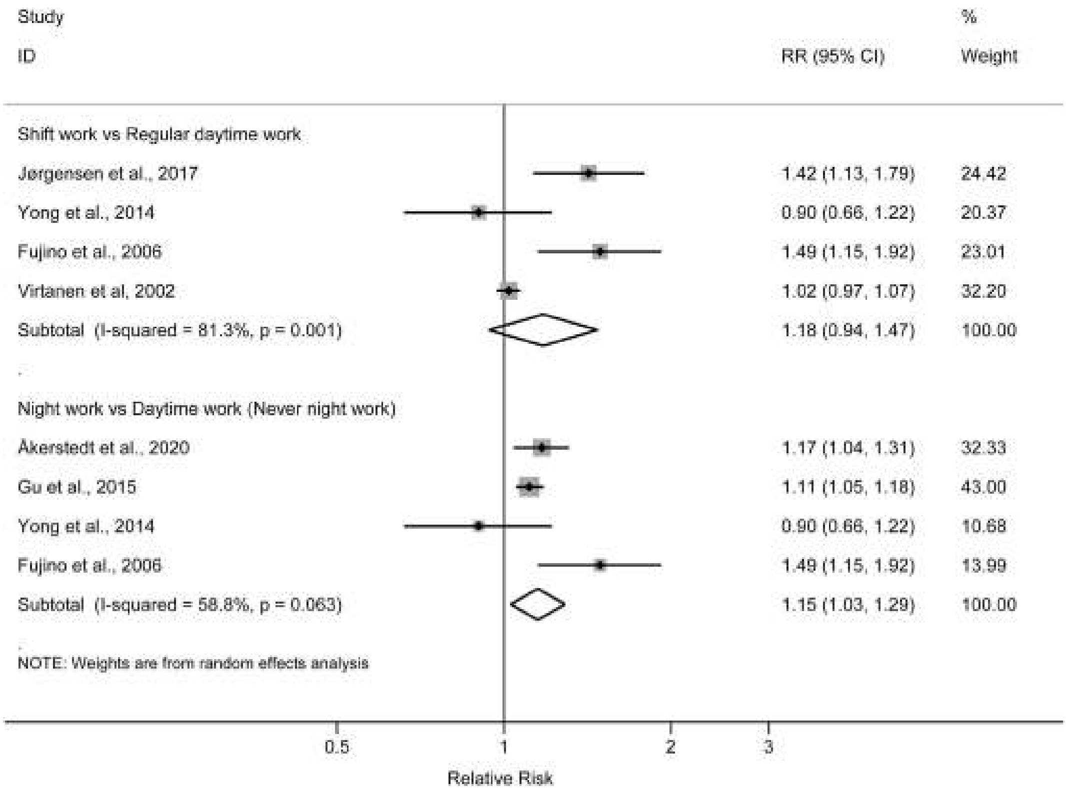


**Fig. 3.** Forest plot for association of shift work and night work with risk of cardiovascular disease mortality.

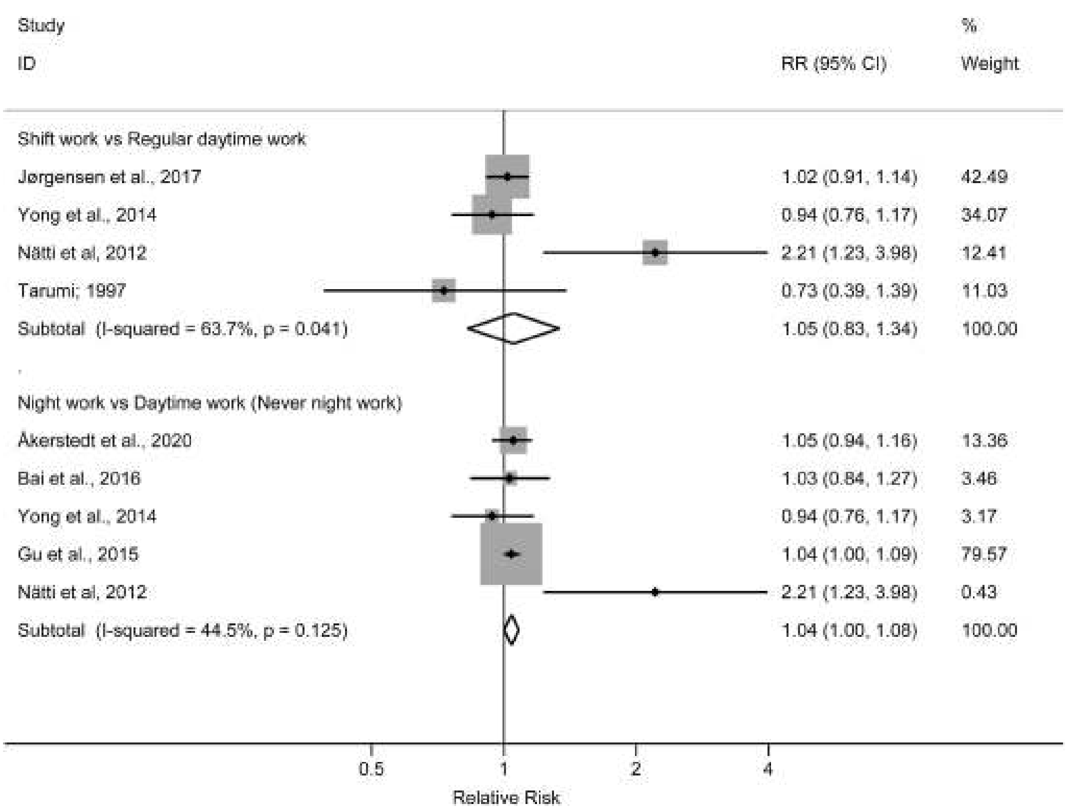


**Fig. 4.** Forest plot for association of shift work and night work and risk of cancer mortality.

Two previous meta-analyses of cohort studies have been conducted to evaluate the association of shift work with risk of mortality [10,45]. Shift work could probably increase the risk of CVD mortality in a dose-response way [45]. Of note, night-shift work was associated with a slightly increased risk of CVD death (pooled RR: 1.027, 95% CI: 1.001–1.053) [45]. Since a limited number of studies were included in the earlier meta-analysis, no significant association for all-cause mortality has been detected [45]. However, the direction of the association was in line with the findings from the current meta-analysis. Furthermore, the current meta-analysis suggested that CVD was the main cause of death for night workers. The increased risk of all-cause mortality may be driven by CVD deaths. The risk of CVD death for night workers was much higher compared with findings from previous meta-analysis [45]. Another previous meta-analysis of four prospective cohort studies found increased risk of death due to CVD-related events associated with shift work [10]. Of note, this study evaluated the risk of death due to CVD subtypes involving MI, CHD and IHD, rather than total CVD events. These evidences further lend confidence to the present findings on the association between night work and risk of total CVD mortality. Besides, the current study also indicated a weak strength of association between night work and risk of cancer mortality. Previous meta-analysis showed that night-shift work may be associated with the incidence and mortality of several major cancers including breast, prostate, colorectal and pancreatic cancers [45–49]. Of note, the association of night work with all-cause mortality may also result from other death causes. A Danish nurse cohort showed that women working night and evening shifts had increased diabetes and Alzheimer's and dementia mortality [6]. Together with previous evidence, the current study provides further support for a link between night work and increased risk of death, especially due to CVD death.

It is generally viewed that night work is most detrimental for health [3]. Shift work may include some non-night shifts as the exposure, which may be one of the explanations for this non-significant association for shift work with risk of death in current study. Possible causal mechanisms between night-shift work and CVD, cancer or other causes of death are still unclear. The alternation between day and night shifts may lead to desynchronization of circadian rhythms [50]. Mismatch of circadian rhythm may cause stress related to sleep deprivation, which may subsequently cause ill health, such as CVD, cancer and metabolic syndrome [50]. Moreover, social stress due to isolation and unfavorable behavioral factors such as cigarette smoking, alcohol drinking and poor quality of diet may together cause severe long-term adverse effects to health [50]. Further studies on the pathophysiology of night work and mortality or health are warranted to confirm the observed association.

The major strength of this meta-analysis is the inclusion of cohort studies, which may expose to lower risk of bias, such as selection and recall bias, compared with case-control or cross-sectional studies. Furthermore, large sample size of the meta-analysis could provide adequate statistical power to detect even a small effect. There are also several limitations in the study. First, there remains the possibility for misclassification of exposure in the included studies. For example, exposure ascertained from job exposure matrixes based on job titles only is regarded as a weak methodology for the estimation of shift work exposure, which may lead to misclassification bias in the original studies. This misclassification of exposure tends to be nondifferential in cohort studies, which could attenuate the risk estimates. Thus, the true overall risk estimates for the associations in the current meta-analysis may be even stronger. Second, although most studies have adjusted for most potential confounders, residual confounding inherent in the original studies may be likely to distort the observed association. However, we cannot address this residual confounding by a meta-analyzed approach. For example, work task and occupation were not considered or adjusted in the multivariable model in the majority of the original studies, which may lead to residual confounding and bias the results. Third, moderate to high level of heterogeneity across the included studies was detected. The heterogeneity may come from various sources, such as different study population (eg, specific group of workers or general working population), various methods of exposure measurement (eg, job exposure matrix or questionnaire), different definitions of the exposure and non-exposure, and different lengths of follow-up, etc. The overall results should be interpreted with caution due to the heterogeneity. Fourth, we did not evaluate the dose-response effects of accumulated exposure (duration or density of shift work) on risk of death since a limited number of original studies reporting available data for the dose-response meta-analysis. Lastly, we cannot rule out the possibility of publication bias. The power of statistical test for publication bias is low when the number of included studies is small [22,23].

In conclusion, this meta-analysis found a significant association between night work and higher risks of all-cause, CVD and cancer mortality, suggesting that night workers, compared with those who never exposed to night work or daytime workers, may have higher risk of death, especially due to CVD. Further well-designed, large-scale interventional studies are warranted to confirm the association. If the association is causal, relevant occupational health policy might be needed to protect workers' health and well-being.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Data availability statements

The datasets during the current study are available from the corresponding author on reasonable request.

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None declared.

## Author contribution

FXS and ZYY developed the research design, interpreted the results, and also had primary responsibility for the final content; FXS, DH and HYW collected and analyzed the data; FXS drafted manuscript; all authors critically reviewed and approved the manuscript.

## Acknowledgement

None.

## Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.08.017.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2021.08.017.

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