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RESEARCH

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

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Abstract

Objective To synthesise the association of shift work with major vascular events as reported in the literature.

Data sources Systematic searches of major bibliographic databases, contact with experts in the field, and review of reference lists of primary articles, review papers, and guidelines.

Study selection Observational studies that reported risk ratios for vascular morbidity, vascular mortality, or all cause mortality in relation to shift work were included; control groups could be non-shift ("day") workers or the general population.

Data extraction Study quality was assessed with the Downs and Black scale for observational studies. The three primary outcomes were myocardial infarction, ischaemic stroke, and any coronary event. Heterogeneity was measured with the I^2 statistic and computed random effects models.

Results 34 studies in 2 011 935 people were identified. Shift work was associated with myocardial infarction (risk ratio 1.23, 95% confidence interval 1.15 to 1.31; I^2=0) and ischaemic stroke (1.05, 1.01 to 1.09; I^2=0). Coronary events were also increased (risk ratio 1.24, 1.10 to 1.39), albeit with significant heterogeneity across studies (I^2=85%). Pooled risk ratios were significant for both unadjusted analyses and analyses adjusted for risk factors. All shift work schedules with the exception of evening shifts were associated with a statistically higher risk of coronary events. Shift work was not associated with increased rates of mortality (whether vascular cause specific or overall). Presence or absence of adjustment for smoking and socioeconomic status was not a source of heterogeneity in the primary studies. 6598 myocardial infarctions, 17 359 coronary events, and 1854 ischaemic strokes occurred. On the basis of the Canadian prevalence of shift work of 32.8%, the population attributable risks related to shift work were 7.0% for myocardial infarction, 7.3% for all coronary events, and 1.6% for ischaemic stroke.

Conclusions Shift work is associated with vascular events, which may have implications for public policy and occupational medicine.

Introduction

Although definitions vary slightly across sources, shift work can be defined as employment in any work schedule that is not a regular daytime schedule (that is, approximately 0900 to 1700).[1] The full spectrum of shift work comprises regular evening or night schedules, rotating shifts, split shifts, on-call or casual shifts, 24 hour shifts, irregular schedules, and other non-day schedules. Shift work has long been known to disrupt circadian rhythm, sleep, and work-life balance; however, flexible work patterns remain a necessary component for a dynamic, diversified industrial economy.[2] The association of shift work with vascular disease is controversial. Conflicting data on this association exist, perhaps in part owing to varying methods, populations, and definitions of shift work and vascular or coronary events.[3] Furthermore, previous syntheses are now outdated, did not use validated tools for assessing studies, did not capture all available data, and did not apply quantitative techniques to compute summary risk estimates.[3-5]

Given these uncertainties, we comprehensively analysed the epidemiology of shift work and vascular events. We were as expansive as possible in our review and did not limit it by study

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Extra material supplied by the author (see http://www.bmj.com/content/345/bmj.e4800?tab=related#webextra) design or type of event analysed. Rather, our goal was to examine reasons for differing estimates in the literature in secondary and sensitivity analyses.

Methods

We planned and reported this systematic review in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[6]

Literature search and selection

We sought observational studies that reported risk ratios (or raw data from which we could derive risk ratios) for the association of shift work with vascular events or mortality. Because of the diversity of endpoints reported, we pre-specified three primary vascular outcomes for this review: myocardial infarction, any coronary event, and ischaemic stroke. Secondary outcomes included heart failure, haemorrhagic stroke, total mortality, cardiovascular mortality, coronary mortality, cerebrovascular mortality, and all cardiovascular events. Outcomes were typically defined by primary study authors using country specific iterations of the international classification of diseases coding system (web extra table A). "Any coronary event" was typically defined as the composite of myocardial infarction, coronary mortality, and hospital admissions due to coronary artery disease (however, certain studies limited their definition to one specific subset of coronary events, such as myocardial infarction or coronary death alone). We imposed no limitation by regional origin, study design, or nature of the control group, which could consist of day workers or the general population.

We systematically searched the following electronic bibliographic databases from their inception until 1 January 2012: Medline including PreMedline, Embase, BIOSIS Previews, Cochrane CENTRAL, Conference Proceedings Citation Index-Science, Google Scholar, ProQuest Dissertation Abstracts, Scopus, and Science Citation Index Expanded. We used database specific subject terms and keywords to generate an initial list of articles for closer scrutiny (extra table B). Two health information specialists (AVI and JC) designed and implemented the search in consultation with the rest of the team. To identify additional studies, we contacted experts in the field, screened reference lists of primary articles and review papers, and did internet searches of occupational medicine and labour department websites. Two reviewers (MVV and DGH) screened citations and rated articles independently for inclusion; disagreements were resolved through consultation with a third reviewer (MM).

Data extraction

We extracted details on study design, setting, definition of shift workers and controls, data sources, accrual interval, outcomes, and follow-up (for cohort studies). We rated methodological quality by using the 27 item Downs and Black scale, which was developed for assessing the design and reporting of both randomised and observational studies.[7] We adapted this scale by removing three items pertaining exclusively to randomised trials (specifically, "blinding of study subjects to the intervention," "randomization to intervention groups," and "concealed randomized intervention assignment").

We classified shift work schedules according to the original study methodological descriptions as evening, night, rotating, mixed, and irregular or unspecified (see extra table A for individual study level definitions). Two reviewers (MVV and DGH) independently extracted all outcome data after redaction of study citation information; subsequently, we consulted study authors about missing or unclear information. We extracted both unadjusted and adjusted risk estimates (where available) together with their confidence intervals or tests of statistical significance.

Statistical analysis

We preferentially pooled multivariable adjusted risk estimates where such estimates were reported; however, if no adjusted analysis was available (n=2 studies), we included the unadjusted estimate. In sensitivity analyses, we separately reported unadjusted and adjusted risk estimates for studies that reported both levels of adjustment. We calculated pooled risk ratios by synthesising across the shift schedules used in individual studies; we used generic inverse variance random effects models with 95% confidence intervals. We used the I^2 statistic to measure heterogeneity; values of 0% to 30% represented minimal heterogeneity, 31% to 50% moderate heterogeneity, and greater than 50% substantial heterogeneity.[8] We assessed our results by using the grading of recommendations assessment, development and evaluation (GRADE) framework.[9]

Because one of the primary outcomes (coronary events) indicated substantial heterogeneity, we used univariate random effects meta-regression to explore potential sources of inconsistency in this outcome. We tested the effects of characteristics of samples, rates of events, region of study, design of study, methodological quality, and whether reported associative measures were adjusted for smoking and socioeconomic status (noted in the occupational literature as important potential confounders for the relation of shift work with coronary events).[10-12] We also did subgroup analyses by type of shift work, overall quality of study (top third of Downs and Black score), adjustment for socioeconomic status, and study design (prospective and retrospective cohort versus case-control), again for coronary events (which represented the most commonly reported outcome) as the outcome variable. In addition, we repeated the primary analysis with Duval and Tweedie's trim and fill analysis (to adjust for potential publication bias).[13] Finally, we calculated the population attributable risk for shift work in terms of the three co-primary outcomes by using data on the prevalence of shift work from the General Social Survey (2010), done by Statistics Canada.[14 15] We used Comprehensive Meta-analysis version 2.0 (Englewood, NJ).

Results

Study selection

After removing duplicates, we identified 12 350 unique references for screening of titles, abstracts, and keywords (web extra figure A). Of these, we retrieved 146 articles in full and rated 35 as eligible for the review (representing 34 distinct datasets).[11 12 16-48] Agreement between reviewers for study inclusion was fair (κ=0.78, 95% confidence interval 0.65 to 0.90).

Study characteristics

The 34 primary samples comprised 2 011 935 people (table 1⇓). Study designs were fairly evenly divided between prospective cohorts (n=11), retrospective cohorts (n=13), and case-control analyses (n=10). Shift schedules were classified as evening shifts (n=4 studies), irregular or unspecified shifts (n=6), mixed schedules (n=11), night shifts (n=9), and rotating shifts (n=10);

seven studies reported more than one category. Most studies (n=30) used non-shift day workers as the referent category, and the remainder used the general population as controls (n=4). The median Downs and Black score expressed as a proportion was 60% (interquartile range 34-86%); the most common deficiencies were a lack of data on contamination of comparison groups (owing to failure to report exposure over multiple time points) and failure to report all types of adverse vascular events potentially related to shift work (extra figure B).

Primary outcomes

Ten studies recorded myocardial infarction, 28 recorded any coronary event, and two recorded ischaemic stroke (table 2⇓ and extra table C). In pooled random effects analyses, shift work status was associated with an increased risk of myocardial infarction (risk ratio 1.23, 95% confidence interval 1.15 to 1.31; I^2=0), coronary events (1.24, 1.10 to 1.39; I^2=85%), and ischaemic stroke (1.05, 1.01 to 1.09; I^2=0) (extra figure C). The I^2 statistic for coronary events suggested substantial heterogeneity (figure⇓). A side by side comparison of unadjusted and adjusted pooled risk ratios from studies reporting both suggested similar results (table 2).

Secondary outcomes

No study reported heart failure or haemorrhagic stroke, so we did not consider these endpoints further. Cardiovascular events, coronary mortality, cerebrovascular mortality, cardiovascular mortality, and all cause mortality were reported by five, nine, four, five, and eight studies. All of these outcomes had risk ratios in excess of 1.0, ranging from 1.04 for all cause mortality to 1.24 for cardiovascular events (table 3⇓, extra figure D); however, none was statistically significant in random effects models at P<0.05.

Sensitivity analyses

The Duval and Tweedie trim and fill analysis continued to indicate an increased risk of myocardial infarction and coronary events even after adjustment for publication bias (this analysis was not possible for ischaemic stroke) (table 2⇓).[21 27] We regressed the log risk ratio of coronary events against various baseline characteristics, as coronary disease was the only heterogeneous outcome of the three primary events. None of the pre-specified characteristics was statistically significant (extra table D). In pooled subgroup analyses, all types of shift work were associated with an increased risk of coronary events, with the exception of evening shift work; the highest point estimate was noted for night shifts (risk ratio 1.41, 1.13 to 1.76) (extra table D). When we isolated studies in the top third of the Downs and Black scores, we continued to observe an increased risk of coronary events (risk ratio 1.18, 1.07 to 1.30). We noted similar findings in studies that adjusted for, matched on, or restricted by socioeconomic status (risk ratio 1.19, 1.04 to 1.36). In addition, prospective cohort studies suggested a higher risk of coronary events (risk ratio 1.32, 1.07 to 1.63) than did retrospective cohort studies (1.19, 1.06 to 1.34) or case-control studies (1.12, 1.003 to 1.25); overall, however, we found no evidence of heterogeneity by study design (P=0.39). Finally, on the basis of the prevalence of shift workers among the adult working population in Canada (32.8%), the population attributable risks related to shift work were 7.0% for myocardial infarction, 7.3% for coronary events, and 1.6% for ischaemic stroke, which represent estimates among people employed in the years 2009 and 2010.

Discussion

In a comprehensive, up to date review of all available literature, we found that shift work was associated with coronary and cerebrovascular events (table 4⇓). We found concordance across statistical models, endpoints, shift work schedules, and adjusted versus unadjusted analyses. Neither publication bias nor socioeconomic status seemed to be a problem.

Strengths and weaknesses

This is the largest synthesis of shift work and vascular risk reported to date. Previous work has been hampered by a narrow focus on only one type of risk (such as coronary disease), a lack of completeness in identifying all relevant studies, absence of quantitative synthesis through conventional meta-analytic techniques, and failure to use a validated tool to assess the quality of studies. We have surmounted these limitations and in addition provide in-depth analyses of methodologically strong studies, the effects of adjusting for socioeconomic status, and comparisons of risk associations against different types of vascular events and different shift work schedules.

On the other hand, several caveats must be noted. As with many meta-analyses of the observational literature, outcome definitions varied somewhat between studies (extra table A); this may have led to heterogeneity in studies' results. Different studies adjusted for different risk factors, although broad consistency between unadjusted and adjusted models was noted. None of the secondary endpoints was statistically significant in relation to shift work, and 95% confidence intervals were wide. The large number of distinct cardiovascular maladies represented under the rubric "cardiovascular events" in various iterations of the international classification of diseases coding system could have caused imprecision in risk for this entity. In addition, ischaemic stroke was reported by only two studies and cerebrovascular mortality by an additional four studies; pooled together, this gives 4592 events (still substantially less than the numbers of coronary events and deaths). In addition, we were unable to discern any major sources for the heterogeneity seen in the outcome of coronary events. Finally, our dataset lacked discrete information on the diurnal type of workers ("morningness" or "eveningness"), so we could not determine whether associations differed across this important characteristic.

Relation to other studies

Notwithstanding these limitations, we have identified an epidemiological association between shift work and vascular events. Unfortunately, observational studies such as those synthesised here cannot definitively prove causality.[49 50] However, other studies have noted that shift workers have higher rates of dyslipidaemia, metabolic syndrome, hypertension, and diabetes.[51-53] Even a single overnight shift is enough to increase blood pressure and impair variability of heart rate.[54]

Shift work is disruptive to circadian rhythm, impairs sleep quality, and affects work-life balance.[55] Insomnia, a complaint common among night shift workers, is an independent risk factor for myocardial infarction.[35] We found that night shifts were associated with the steepest increase in risk for coronary events (risk ratio 1.41, 95% confidence interval 1.13 to 1.76). Shift workers are also more likely to smoke and often have worse socioeconomic status than do day workers, although presence or absence of adjustment for these factors was not a source of heterogeneity in our analyses; accordingly, subgroup analyses limited to studies that accounted for social class still indicated an increase in coronary risk.[56 57] Certainly, to the extent that shift work selects for people with worse lifestyle related habits, it could be a marker rather than a cause of vascular disease. Yet an increased risk of vascular events was evident even in studies that adjusted for unhealthy behaviours in shift workers.[21 24 26 30 35 45] Unhealthy behaviour alone thus cannot fully account for the association between shift work and cardiovascular events.

Some data suggest that shift work is associated with neoplasia. Hansen and Lassen recently reported an increased risk of breast cancer among female military employees working night shifts; they observed a clear dose-response relation according to the number of years of night shift work (P=0.03) and the cumulative number of such shifts (P=0.02).[58] People in the highest third of exposure had a more than twofold increase in the odds of breast cancer (multivariable adjusted odds ratio 2.3, 1.2 to 4.6). Intriguingly, women with morning chronotype preference and exposure to night work greater than the median had even higher risks (adjusted odds ratio 3.9, 1.6 to 9.5). This last finding may suggest a role for disruption of circadian rhythm in the pathogenesis of shift work associated breast cancer.

Study implications

Our findings have several implications. The increased risk of vascular disease apparent in shift workers, regardless of its explanation, suggests that people who do shift work should be vigilant about risk factor modification. Screening programmes for modifiable risk factors in shift workers have yielded substantial burdens of treatable risk factors, including dyslipidaemia, smoking, glucose intolerance, and hypertension.[59-63] Shift workers should be educated about cardiovascular symptoms in an effort to forestall or avert the earliest clinical manifestations of disease. Evidence also exists in the literature to suggest that modification and rationalisation of shift schedules may yield dividends in terms of healthier, more productive workers; however, the long term effects of these alterations on vascular outcomes remain unknown.[64-66] More work is needed to identify the most vulnerable subsets of shift workers and the effects of shift modifying strategies on overall vascular health.

Contributors: MVV, JC, and DGH were involved in conception and design of the study. MVV, DGH, IJ, LEL, AVI, JC, and MM were responsible for data acquisition. MVV, DGH, AXG, GP, and AD analysed and interpreted the data. MVV and DGH drafted the manuscript, which was critically revised for important intellectual content by all authors. MVV, DGH, and AD did the statistical analysis. DGH obtained funding. JC and AVI provided administrative, technical, or material support. DGH supervised the study and is the guarantor.

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Ethical approval: Not needed.

Data sharing: Technical appendix, statistical code, and dataset are available from the corresponding author (dhackam@uwo.ca).

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What is already known on this topic

Shift work is associated with an increased risk of hypertension, metabolic syndrome, dyslipidaemia, and diabetes mellitus

Disruption of circadian rhythm may predispose shift workers to vascular events; however, no organised systematic synthesis of all types of vascular events is available

What this study adds

Shift work is associated with myocardial infarction, coronary events, and ischaemic stroke; the relative risks are modest, but population attributable risks are high

These findings seem to be robust and insensitive to publication bias, quality of study, and socioeconomic status

Conversely, shift work is not associated with increased rates of mortality (whether vascular cause specific or overall)

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Tables

Table 1| **Characteristics of studies**

Study	Design*	Setting/data source	Sample	Outcomes	Variables accounted for
Akerstedt et al, 2004	Retrospective cohort	Swedish Living Conditions Survey	22 411	All cause mortality	Age, stress, physically strenuous work, smoking, chronic disease
Alfredsson et al, 1985	Retrospective cohort	Swedish census data	958 096	Myocardial infarction	Age, county
Allesoe et al, 2011	Prospective cohort	Danish Nurse Cohort Study	12 116	Coronary events	Age, family history, diabetes, menopause, BMI, smoking, alcohol consumption, leisure time activity, physical activity at work
Babisch et al, 2005	Case-control	32 major hospitals in Berlin, Germany	4115	Myocardial infarction	Age, diabetes, hypertension, family history, smoking, BMI, employment status, living without a partner, noise sensitivity, education, sex†, hospital†
Biggi et al, 2008	Retrospective cohort	Municipal workers in Milan, Italy	468	Coronary events	No covariate adjustment
Boggild et al, 1999	Prospective cohort	Copenhagen Male Study	5207	Coronary events, all cause mortality	Age, social class, sleep, tobacco, weight, height, fitness
Brown et al, 2009	Prospective cohort	Nurses' Health Study	80 108	Ischaemic stroke	Age, questionnaire cycle, physical activity, BMI, alcohol, fruit and 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	Retrospective cohort	Employees of fertilizer plant in Doha, Qatar	2562	Coronary and cardiovascular events	No covariate adjustment
Falger and Schouten, 1992	Case-control	Two large hospitals in Netherlands	458	Myocardial infarction	Age, exhaustion, smoking, education, hospital site†
Fujino et al, 2006	Prospective cohort	Survey data in Japan	17 649	Coronary, cardiovascular, cerebrovascular, and all cause mortality	Age, smoking, alcohol, education, perceived stress, past medical history, BMI, hours of walking, hours of exercise, job type
Fukuoka et al, 2005	Case-control	Five hospitals in Japan	94	Myocardial infarction	Age†, work status†, sex†
Haupt et al, 2008	Retrospective cohort	Survey data in West Pomerania, Germany	2510	Myocardial infarction	Age, sex, food frequency score, socioeconomic status, smoking
Hermansson et al, 2007	Case-control	Survey data in Sweden	607	Ischaemic stroke	Age, smoking, education, job strain, BP, serum triglycerides, cholesterol, sex†, survey†, survey date†, locale
Hublin et al, 2010	Prospective cohort	Population based twin cohort in Finland	20 142	Coronary mortality, cardiovascular events	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 tranquillisers, physical workload, working pace
Karlsson et al, 2005	Retrospective cohort	Pulp and paper workers in Sweden	5442	Coronary, stroke related, and all cause mortality	Age, duration of employment
Kawachi et al, 1995	Prospective cohort	Nurses' Health Study	79 109	Myocardial infarction, coronary events, coronary and all cause mortality, cardiovascular events	Age, smoking, diabetes, hypertension, hypercholesterolaemia, past oral contraceptive use, current use of hormonal replacement, parental MI before age 60, alcohol, physical activity, BMI, aspirin use, fifths of vitamin E, follow-up period, husband's education
Knutsson et al, 1986	Prospective cohort	Pulp and paper works in Sweden	504	Coronary events	Age, duration of exposure, smoking, family status
Knutsson et al, 1999	Case-control	Survey data in Sweden	4648	Myocardial infarction	Age†, sex†, residence†, smoking, job strain, education
Koller, 1983	Retrospective cohort	Oil refinery workers in Austria	301	Coronary and cardiovascular events	Age†, duration of employment†
Laugsand et al, 2011	Prospective cohort	Nord-Trøndelag Health Study (survey in Norway)	52 610	Myocardial infarction	Age, sex, marital status, education, shift work, systolic blood pressure, total cholesterol, diabetes mellitus, BMI, physical activity, smoking, depression, poor sleep

Table 1 (continued)

Study	Design*	Setting/data source	Sample	Outcomes	Variables accounted for
Liu and Tanaka, 2002	Case-control	22 hospitals in Japan	705	Myocardial infarction	Age†, sex†, residence†
McNamee et al, 1996	Case-control	Nuclear plant workers	934	Coronary mortality	Age†, smoking, BMI, height, systolic BP, diastolic BP, job status, duration of employment, year of starting work†
Netterstrom et al, 1999	Case-control	Two Danish hospitals	252	Myocardial infarction	Age†, sex†
Rafnsson and Gunnarsdottir, 1990	Retrospective cohort	Fertiliser plant workers in Iceland	603	Coronary and all cause mortality	Age, calendar year
Steenland and Fine, 1996	Case-control	Heavy equipment plant workers (US)	944	Coronary mortality	Age, worksite, race
Tarumi, 1997	Retrospective cohort	Japanese steel industry workers	9141	Cardiovascular and all cause mortality	Age, job site location, blue collar status†
Taylor and Pocock (reanalysed by Knutsson et al, 2004)	Retrospective cohort	10 industrial organisations in Britain	8767	Coronary and cerebrovascular mortality, cardiovascular and total mortality	Age, calendar period, sex†
Taylor et al, 1972	Retrospective cohort	29 industrial organisations in Britain	1930	Cardiovascular events	Age†, organisation†, occupation†
Tuchsen, 1993	Prospective cohort	Danish survey data	406 969	Coronary events	Age, sex†
Tuchsen et al, 2006	Prospective cohort	Danish survey data	5517	Coronary and cardiovascular events	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
Vertin, 1978	Prospective cohort	Viscose rayon factory workers	200	Coronary events	Carbon disulfide exposure†
Virkunnen et al, 2006	Prospective cohort	Helsinki Heart Study (clinical trial)	1804	Coronary events	Age, smoking, systolic BP, cholesterol, BMI, gemfibrozil use, noise, physical workload
Virtanen and Notkola, 2002	Retrospective cohort	Finnish census data	385 500	Cerebrovascular and cardiovascular mortality	Age, marital status, professional status, education, income, socioeconomic status, job exposure variables
Yadegarfar and McNamee, 2008	Case-control	Nuclear plant workers in Britain	1270	Coronary mortality	Age†, year of starting work†, smoking, systolic BP, diastolic BP, BMI, height, work status, duration employment, social class

BMI=body mass index; BP=blood pressure.

*All studies used day workers as comparison group, with four exceptions that used general population controls—Alfredsson et al, Rafnsson et al, Taylor et al, and Tuchsen 1993.

†Matching or stratifying variable.

Table 2| **Primary outcomes**

Analysis	Events (studies)	Risk ratio (95% CI)	I^2
Random effects*			
Myocardial infarction	6598 (10)†	1.23 (1.15 to 1.31)	0%
All coronary events	17 359 (28)†	1.24 (1.10 to 1.39)	85%
Ischaemic stroke	1854 (2)†	1.05 (1.01 to 1.09)	0%
Sensitivity analyses‡			
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%
Ischaemic stroke, unadjusted	1854 (2)	1.09 (1.04 to 1.14)	0%
Ischaemic stroke, adjusted	1854 (2)	1.05 (1.01 to 1.09)	0%
Trim and filled estimates			
Myocardial infarction	(12)§	1.22 (1.15 to 1.30)	NA
All coronary events	(32)§	1.19 (1.06 to 1.34)	NA
Ischaemic stroke¶	—	—	—

NA=not applicable.

*These analyses preferentially pooled adjusted risk estimates, with unadjusted estimates included only for studies that reported crude estimates alone.

†Random effects mean event risks for myocardial infarction, coronary events, and ischaemic stroke were 0.8%, 2.9%, and 2.1% (totalled over follow-up for cohort studies).

‡These analyses pooled subset of studies that reported both unadjusted and adjusted risk estimates.

§Includes hypothetical unpublished studies imputed to left of mean.

¶Duvall and Tweedie's trim and fill method could not be applied, as only two studies were reported.

Table 3| **Secondary outcomes**

Outcome*	Events (studies)	Event risk†	Random effects risk ratio (95% CI)	Fixed effects risk ratio (95% CI)	I^2
Cardiovascular events	1423 (5)	6.4%	1.24 (0.81 to 1.89)	1.30 (1.13 to 1.50)	85%
Coronary mortality	3166 (9)	1.8%	1.08 (0.97 to 1.21)	1.07 (0.99 to 1.17)	29%
Cerebrovascular mortality	2738 (4)	1.0%	1.12 (0.89 to 1.40)	1.12 (0.99 to 1.28)	52%
Cardiovascular mortality	17 335 (5)	1.2%	1.14 (0.98 to 1.32)	1.04 (0.99 to 1.09)	65%
All cause mortality	8092 (8)	8.0%	1.04 (0.97 to 1.11)	1.03 (0.98 to 1.09)	36%

*See web extra table A for study level definitions.

†Random effects mean event risk totalled over follow-up for cohort studies.

Table 4| **Summary of findings: is shift work associated with an increased risk of cardiovascular events?***

Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	No of participants (studies)	Relative effect (95% CI)	Quality of evidence (GRADE)
Myocardial infarction	Not likely†	No serious inconsistency‡	No serious indirectness§	No serious imprecision¶	Not likely**	1 082 977 (10)	1.23 (1.15 to 1.31)	Moderate††⊕⊕⊕O
Coronary events	Not likely†	Inconsistency‡‡	No serious indirectness§	No serious imprecision¶	Not likely**	1 530 070 (28)	1.24 (1.10 to 1.39)	Low††⊕⊕ OO
Ischaemic stroke	Not likely†	No serious inconsistency‡	No serious indirectness§	No serious imprecision¶	Undetected§§	80 787 (2)	1.05 (1.01 to 1.09)	Moderate†† ⊕⊕⊕O

†Median Downs and Black score for included studies was 60% (interquartile range 34-86%).

‡I^2=0%.

§Population, outcome, and intervention were consistent with question of interest, although individual studies varied.

¶No of events and participants studied in review is large, and confidence interval does not include null value.

**Estimates adjusted for publication bias did not differ from observed estimates.

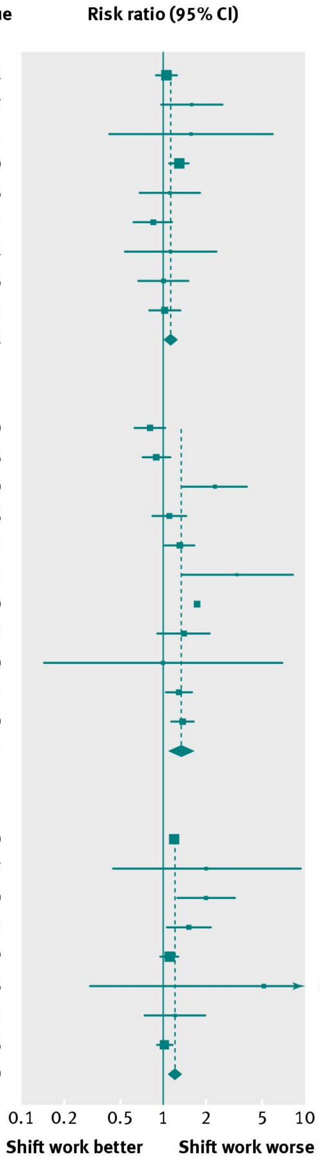
††Dilution effect of single time point exposure ascertainment allows upgrading of evidence.

‡‡I^2=85%.

§§Publication bias could not be tested for two studies.

Figure

Study	z score	P value	Risk ratio (95% CI)
Case control studies			
Babisch et al	0.61	0.54	1.05 (0.89 to 1.25)
Falger and Schouten	1.80	0.07	1.59 (0.96 to 2.64)
Fukuoka et al	0.66	0.51	1.57 (0.41 to 5.98)
Knutsson 1999	3.12	0.00	1.30 (1.10 to 1.53)
Liu and Tanaka	0.44	0.66	1.12 (0.68 to 1.83)
McNamee et al	-0.98	0.33	0.85 (0.61 to 1.18)
Netterstrom et al	0.33	0.74	1.13 (0.54 to 2.39)
Steenland et al	0.05	0.96	1.01 (0.67 to 1.53)
Yadegarfar and McNamee	0.22	0.82	1.03 (0.80 to 1.33)
Total	2.01	0.04	1.12 (1.00 to 1.25)
Prospective cohort studies			
Allesoe et al	-1.65	0.10	0.81 (0.63 to 1.04)
Boggild et al	-0.91	0.36	0.90 (0.72 to 1.13)
Fujino et al	3.12	0.00	2.32 (1.37 to 3.94)
Hublin et al	0.73	0.46	1.11 (0.84 to 1.47)
Kawachi et al	2.12	0.03	1.31 (1.02 to 1.68)
Knutsson 1986*	2.58	0.01	3.32 (1.33 to 8.26)
Tuchsen 1993	20.18	0.00	1.74 (1.65 to 1.84)
Tuchsen et al 2006	1.54	0.12	1.40 (0.91 to 2.15)
Vertin	0.00	1.00	1.00 (0.14 to 6.96)
Virkunnen et al	2.35	0.02	1.30 (1.04 to 1.62)
Laugsand et al	3.28	0.00	1.37 (1.14 to 1.66)
Total	2.58	0.01	1.32 (1.07 to 1.63)
Retrospective cohort studies			
Alfredsson et al	3.95	0.00	1.20 (1.09 to 1.31)
Biggi et al	0.90	0.37	2.02 (0.43 to 9.40)
Ellingsen et al	2.82	0.00	1.99 (1.23 to 3.22)
Haupt et al	2.26	0.02	1.53 (1.06 to 2.21)
Karlsson et al	1.30	0.19	1.11 (0.95 to 1.30)
Koller	1.13	0.26	5.17 (0.30 to 89.43)
Rafnsson and Gunnarsdottir	0.76	0.45	1.21 (0.74 to 1.98)
Taylor and Pocock	0.43	0.66	1.03 (0.90 to 1.18)
Total	2.94	0.00	1.19 (1.06 to 1.34)



Meta-analysis of coronary events. Studies were combined using a random effects generic inverse variance model after stratification by study design. *Risk ratio and 95% confidence interval recalculated from original study data over duration of follow-up