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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<sup>2</sup> 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<sup>2</sup>=0) and ischaemic stroke (1.05, 1.01 to 1.09; I<sup>2</sup>=0). Coronary events were also increased (risk ratio 1.24, 1.10 to 1.39), albeit with significant heterogeneity across studies (I<sup>2</sup>=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).<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>3 4 5</sup>

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 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).<sup>6</sup>

## 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 (MMV 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.<sup>7</sup> 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 (MMV 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.<sup>8</sup> We assessed our results by using the grading of recommendations assessment, development and evaluation (GRADE) framework.<sup>9</sup>

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).<sup>10-11-12</sup> 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).<sup>13</sup> 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.<sup>14-15</sup> 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).<sup>11 12 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48</sup> Agreement between reviewers for study inclusion was fair ( $\kappa=0.78$ , 95% confidence interval 0.65 to 0.90).

## Study characteristics

The 34 primary samples comprised 2011935 people (table 1 [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 ( $n=8$ ), 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 dayworkers 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 80% (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).

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Table 1  
Characteristics of studies

## Primary outcomes

Ten studies recorded myocardial infarction, 28 recorded any coronary event, and two recorded ischaemic stroke (table 2 [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 [figure 1](#)). A side by side comparison of unadjusted and adjusted pooled risk ratios from studies reporting both suggested similar results (table 2).



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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

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Table 2  
Primary outcomes

## 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 3B, extra figure D); however, none was statistically significant in random effects models at  $P < 0.05$ .

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Table 3

## 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†).<sup>21 27</sup> 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.

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Table 4

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

## 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.<sup>49–50</sup> However, other studies have noted that shift workers have higher rates of dyslipidaemia, metabolic syndrome, hypertension, and diabetes.<sup>51–52–53</sup> Even a single overnight shift is enough to increase blood pressure and impair variability of heart rate.<sup>54</sup>

Shift work is disruptive to circadian rhythm, impairs sleep quality, and affects work-life balance.<sup>55</sup> Insomnia, a complaint common among night shift workers, is an independent risk factor for myocardial infarction.<sup>35</sup> 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.<sup>56–57</sup> 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.<sup>21–24–26–30–35–45</sup> 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 ( $P=0.02$ ).<sup>53</sup> 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.<sup>59–60–61–62–63</sup> 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.<sup>64–65–66</sup> More work is needed to identify the most vulnerable subsets of shift workers and the effects of shift modifying strategies on overall vascular health.

## 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)

## Footnotes

- Contributors: MW, JC, and DGH were involved in conception and design of the study. MW, DGH, U, LEL, AM, JC, and MM were responsible for data acquisition. MW, DGH, AXG, GP, and AD analysed and interpreted the data. MW and DGH drafted the manuscript, which was critically revised for important intellectual content by all authors. MW, DGH, and AD did the statistical analysis. DGH obtained funding. JC and AM 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 ([dheekam@uwo.ca](mailto:dheekam@uwo.ca)).

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