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IN-DEPTH REVIEW

Shift work and chronic disease: the epidemiological evidence

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Background Shift work, including night work, has been hypothesized to increase the risk of chronic diseases, including cancer, cardiovascular disease (CVD), metabolic syndrome and diabetes. Recent reviews of evidence relating to these hypotheses have focussed on specific diseases or potential mechanisms, but no general summary of the current data on shift work and chronic disease has been published.

Methods Systematic and critical reviews and recent original studies indexed in PubMed prior to 31 December 2009 were retrieved, aided by manual searches of reference lists. The main conclusions from reviews and principle results from recent studies are presented in text and tables.

Results Published evidence is suggestive but not conclusive for an adverse association between night work and breast cancer but limited and inconsistent for cancers at other sites and all cancers combined. Findings on shift work, in relation to risks of CVD, metabolic syndrome and diabetes are also suggestive but not conclusive for an adverse relationship.

Conclusions Heterogeneity of study exposures and outcomes and emphasis on positive but non-significant results make it difficult to draw general conclusions. Further data are needed for additional disease endpoints and study populations.

Key words Cancer; cardiovascular disease; circadian disruption; diabetes; light at night; melatonin; metabolic syndrome; night work; shift work.

Introduction

'Shift work' is a work schedule involving irregular or unusual hours, compared to those of a normal daytime work schedule. Many different work schedules can be described as shift work, including night work and rotating shift work. A recent report on working conditions showed that ~20% of the European working population are involved in some form of shift work [1]. Shift work has been implicated as a risk factor for a number of chronic diseases, including breast cancer, cancers at other sites, cardiovascular disease (CVD) and other related chronic conditions.

Epidemiological research on the association between shift work and cancer has primarily focussed on the potential negative effects of night work. The light at night and melatonin hypothesis has received particular attention and proposes that light at night suppresses the secretion of endogenous melatonin, and this in turn may influence risk of cancer through a number of direct and indirect pathways [2–4]. More recently, there has been a wider interest in the roles of circadian rhythm disruption, long-term sleep disruption and deprivation, immune depression, and desynchronization of clock genes caused by shift work in the development of cancer [5,6]. Shift work has also been hypothesized to contribute to development of CVD and other metabolic disorders through a number of pathways including circadian rhythm disruption, lifestyle changes, job strain and stress, and social stress [7,8].

Recent reviews of the epidemiological evidence for the association between shift work and chronic disease have focussed on specific associations, such as night shift work and cancer and shift work and ischaemic heart disease (IHD). No general summary of the evidence for associations between shift work and chronic disease has been published. To update researchers and occupational physicians on the current knowledge of the field and to inform guidelines and policies, a wide-ranging discussion of shift work and chronic disease is necessary. A broader review is also warranted of the commonalities (some of the putative mechanisms, challenges in study design and data interpretation) shared by the studies of the associations of shift work with different chronic disease endpoints. This review explores the current evidence from systematic and

critical reviews and recent new data. The underlying mechanisms are discussed, based on results and hypotheses summarized from both epidemiological and *in vitro* studies.

Methods

This is a secondary review of the literature on shift work and chronic disease, identifying results from existing systematic reviews and more recent publications of original data. The literature indexed in PubMed prior to 31 December 31 2009 was searched combining key words for shift work ('work schedule tolerance' or 'shift work') with key words for each of the chronic diseases or conditions of interest (e.g. 'cancer') and other key words ('survival rate' or 'mortality' or 'morbidity' or 'odds ratio' or 'incidence' or 'risk'). In total, this provided 550 search results. Articles not written in English, not reporting findings on human subjects, reporting clinical trials or practice guidelines or randomized controlled trials, or which did not have an available abstract were then excluded. The titles and abstracts of the papers identified were then assessed for their potential relevance. Studies were included if they were epidemiological studies with the exposed group consisting of shift workers and the reference group consisting of day workers or workers who predominantly worked day shifts. Reference lists of the retrieved publications were also searched manually to identify any additional publications matching the inclusion criteria. Original studies were assessed if they had not been included in any of the identified systematic reviews. In this review, the term 'shift work' was used to refer to any work schedule involving unusual or irregular working hours as opposed to a normal daytime work schedule.

Main conclusions from the reviews are summarized. Recent original studies that have not been included or summarized quantitatively by any of the reviews are reported and discussed in more detail. The assessment of the strength of the evidence was made with the modified Royal College of General Practitioners (RCGP) three-star system [9] (Box 1).

Box 1. The modified RCGP three-star system

- '***' Strong evidence — provided by generally consistent findings in multiple, high-quality scientific studies;
- '**' Moderate evidence — provided by generally consistent findings in fewer, smaller, or lower quality scientific studies;
- '*' Limited or contradictory evidence — provided by one scientific study or inconsistent findings in multiple scientific studies and
- '–' No scientific evidence — based on clinical studies, theoretical considerations and/or clinical consensus.

Results

Cancer

The details of the recent reviews and reports identified on shift work and the risk of cancer are summarized in Table 1. In 2007, an expert working group convened by the International Agency for Research on Cancer (IARC) concluded that 'shift-work that involves circadian disruption is probably carcinogenic to humans' on the basis of 'limited evidence in humans for the carcinogenicity of shift-work that involves night work' and 'sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)' [10]. Epidemiological studies contributing to this conclusion examined the risk of breast cancer in shift workers [11–18] and in flight attendants [19].

In 2008, Kolstad [20] published a comprehensive critical review of the relationship between night shift work and the risk of breast cancer and other cancers. The review concluded that the data on the positive association between long-term night work and risk of breast cancer were suggestive but still limited; the data on the association between night shift work and risk of cancers at other sites (including cancers of the prostate and colon) and of cancer overall were insufficient. The review also discussed several problems with the existing literature, including insufficient and inconsistent inclusion of potential confounding factors in analyses, and selection bias.

Breast cancer

Previous studies on the relationship between night shift work and cancer have mainly focussed on breast cancer [19,21,22]. In 2005, Megdal *et al.* [19] carried out a meta-analysis of the data on night shift work and breast cancer (including studies of airline cabin crews and other night shift workers) and reported a summary relative risk (RR) of 1.48 (95% confidence interval (CI) 1.36–1.91) for all studies combined. The expert working group at IARC identified eight studies of night shift work and breast cancer, six of which noted modestly increased risk of breast cancer in long-term night workers compared with those who were not engaged in shift work at night [10]. Two of these studies reported data from prospective studies of nurses engaged in night work. The first, from the Nurses' Health Study in the United States, estimated that nurses reporting ≥30 years of rotating night shifts

Table 1. Recent epidemiological studies and reviews on the relationship between shift work and cancer

Authors	Study	Findings
Cancer		
Lahti *et al.* [26]	Cohort study of general population in Finland with non-Hodgkin's lymphoma as outcome and 10 year-lagged cumulative night shift work as exposure. F: cases: 1337 unexposed, 1157 exposed; M: cases: 2286 unexposed, 1527 exposed (25–64 at census).	RR = 1.10 (95% CI 1.03–1.19) in men; RR = 1.02 in women (95% CI 0.94–1.12). Covariates were age, social class, cohort period.
Review		
Straif *et al.* [10]	Summary of findings by the International Agency for Research on Cancer (IARC) working group on the carcinogenicity of shift work.	On the basis of 'limited evidence in humans for the carcinogenicity of shift work that involves night work' and 'sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)', the working group concluded that 'shift work that involves circadian disruption is probably carcinogenic to humans'.
Megdal *et al.* [19]	Night work and breast cancer: a systematic review of 13 studies, 7 of which are on airline cabin crew.	Night work was associated with an increased risk of breast cancer.
Kolstad [20]	A systematic review on the relationship between night shift work and breast cancer and other cancers: of 13 studies included, 8 studies looked at breast cancer, 3 at prostate cancer, 3 at colon cancer and 4 at all cancers combined.	Based on data published to May 2007, concluded that there was suggestive but not conclusive evidence that long-term night shift work (≥20 years) increased the risk of breast cancer. There was a lack of evidence on the association of night shift work and risk for cancer at other sites.
Hansen [22]	Discussion of previous evidence and ongoing studies in Denmark focussing on the relationship between melatonin, night shift work and breast cancer.	Previous evidence was relatively consistent for an increased risk of breast cancer in women working at non-day time.
Davis and Mirick [21]	Discussion of previous evidence and ongoing studies in Seattle (United States), focussing on the relationship between light at night, night shift work and breast cancer.	Evidence from the studies carried out in Seattle supported the hypothesis that the exposure to night work is associated with an increased risk of breast cancer.

F, female; M, male.

were 36% more likely to get breast cancer than those who did not report working rotating night shifts (RR = 1.36, 95% CI 1.04–1.78) [13]. In the Nurses' Health Study II, women who reported ≥20 years of rotating night shifts had an elevated risk for breast cancer compared with women who did not report working rotating night shifts (RR = 1.79, 95% CI 1.06–3.01) [15].

Kolstad [20], however, provided a more cautious interpretation of the published data than the summary from the IARC working group, concluding that while there were some indications that long-term night work might increase risk, overall there was only limited evidence for an association between night shift work and breast cancer. Kolstad [20] also highlighted the problems in the existing data including the limited number of studies on the topic, the generally small magnitude of the reported association, and that the predominant positive and prospective data are only available for one occupational group (nurses). To date, there have been no further reports with new data on the relationship between night work and risk of breast cancer.

Prostate cancer

There is limited and inconsistent evidence for an association between shift work and prostate cancer, based on three epidemiological studies [18,23,24]. Kolstad [20] described the results from these three papers, but only discussed data from Kubo *et al.* [23] and Conlon *et al.* [24] in detail. Kubo *et al.* [23] reported that men on rotating shifts were three times more likely to develop prostate cancer than men on daytime shifts in a prospective study. Consistent with these findings, a case–control study presented in Conlon *et al.* [24]

found an association between ever having worked a full-time rotating shift and an increased risk of prostate cancer. In contrast, Schwartzbaum *et al.* [18] did not find a significant association between shift work and prostate cancer.

Colorectal cancer

Evidence for an association between shift work and colorectal cancer is also limited and inconsistent. Data from the published studies were reviewed in Kolstad [20], although only results in men from Schwartzbaum *et al.* [18] were presented. In this Swedish general population cohort study, no significant association was found between shift work and colon or colorectal cancer in both men and women, which was similar to the findings from an earlier Norwegian study on telegraph operators [11]. In contrast, findings from the Nurses' Health Study showed that nurses who worked 15 years or more on rotating night shifts with at least three working nights per month had moderately increased risk for colorectal cancer [25].

Cancer at other sites

Only one study has been published on the relationship between shift work and risk of cancer at a site other than those discussed above. Lahti *et al.* [26] investigated 3813 men and 2494 women who developed non-Hodgkin lymphoma during follow-up in a Finnish population-based cohort of 1 669 272 individuals. They found nighttime work to be significantly associated with an increased risk of non-Hodgkin lymphoma in men (RR = 1.10, 95% CI 1.03–1.19) but not in women (RR = 1.02, 95% CI 0.94–1.12).

Cancer at all sites combined

Four studies have examined the relationship between shift work and overall cancer risk (mortality or incidence), but none provides strong evidence for a positive association [11,18,27,28]. Kolstad [20] reviewed the four studies but did not describe the data on women reported by Schwartzbaum *et al.* [18], in which the standardized incidence ratio for cancer at all sites combined was 1.00 (95% CI 0.89–1.13) in women and 1.02 (95% CI 1.00–1.05) in men, for shift workers in comparison to non-shift workers.

Overall, there is suggestive evidence for an association between long-term night work (≥20 years) and an increased risk of developing breast cancer and we grade the epidemiological evidence as moderate (RCGP **). However, the data for an association with cancers at other sites and all cancers combined are limited and inconsistent, and few studies have examined associations of cancer risk with types of shift work other than night work. On the basis of the modified RCGP system, we grade the epidemiological evidence for the associations between shift work and cancers at other sites and all cancers combined as limited (*).

Cardiovascular disease

The details of the critical reviews and recent reports identified on shift work and the risks of CVD are summarized in Table 2. An early review highlighted the possibility of adverse effects of shift work on the cardiovascular system [29]. Two later summaries concluded that a 40% increase in CVD reported by Knutsson *et al.* [30] in shift workers compared to day workers provided a reasonable estimate for the adverse association [31,32]. In contrast to these reports, a more recent systematic review of the relationship between shift work and IHD concluded that the published findings on shift work and IHD were inconclusive and did not support a causal association [7].

The recently published data on shift work and CVD are inconsistent but overall provide some support for an adverse association, with three studies reporting an increased risk and one finding no significant associations (Table 2). Ellingsen *et al.* [33] reported an increased risk of coronary heart disease among shift workers (RR = 1.65, 95% CI 1.38–1.97), but the published paper did not report the study design and the model adjustments clearly. Haupt *et al.* [34] reported an increased risk of myocardial infarction among shift workers versus non-shift workers [hazard ratio (HR) = 1.53, 95% CI 1.06–2.22] using outcome and time-at-risk data collected in the same cross-sectional survey. Two studies focussed on ischaemic stroke: Hermansson *et al.* [35] did not find an increased risk of ischaemic stroke among shift workers (RR = 1.0, 95% CI 0.6–1.8), while in the Nurses' Health Study, there was a small increased risk of ischaemic stroke in nurses who reported working rotating night shifts for 15 or more years (HR = 1.04, 95% CI 1.01–1.07) [36].

Overall for CVD, the systematic and critical reviews provide suggestive but not conclusive evidence for a significant association with shift work, including night and rotating shift work [7,29,31,32]; new results add some support for an adverse association. According to the modified RCGP system, we grade the epidemiological evidence for the association between shift work and CVD as moderate (**).

Metabolic syndrome and diabetes

Metabolic syndrome

Metabolic syndrome is a cluster of risk factors including central obesity, elevated blood pressure, elevated triglycerides, lowered high-density lipoprotein cholesterol and elevated fasting glucose, which are often seen simultaneously in an individual [37]. The criteria for diagnosis

Table 2. Recent epidemiological studies and reviews on the relationship between shift work and CVD and related chronic conditions

Authors	Study design	Population (age)	Population and occupation (Location)	Outcomes	Main exposure/ referents	Main results	Covariates
CVD							
Ellingsen *et al.* [33]	'Case series of cohort'[a]	M: 223 cases: CAD or MI—27 shift workers, 40 day workers; other atherogenic vascular diseases—61 shift workers, 95 day workers	Workers in a fertiliser plant (Qatar)	CAD or MI; other atherogenic vascular diseases	Rotating shift work (8 h rotating shift: 2 mornings, 2 afternoons, 2 nights and 2 days of rest)/day work	RR = 1.65 (95% CI 1.38–1.97) of cardiovascular events.	Model adjustments not specified, but implied using S, BMI, diabetes, senior or intermediate staff
Hermansson *et al.* [35]	Nested case-control	F: 65 day worker cases, 23 shift worker cases; 136 day worker controls, 49 shift worker controls; M: 85 day worker cases, 21 shift worker cases, 183 day worker controls, 45 shift worker controls (mean age: 54.7)	Combination of two population-based health surveys (Sweden)	Ischaemic stroke	Shift work/day work	RR = 1.0 (95% CI 0.6–1.8) of ischaemic stroke	Age-adjusted. Other models with similar results: (1) age, job strain, S, low educational level; (2) high serum triglycerides, high serum total cholesterol, high BP
Haupt *et al.* [34]	Cross-sectional	F: 1052 unexposed, 192 exposed; M: 760 unexposed, 506 exposed (mean age: 61.5 unexposed, 62.3 exposed)	Adult population in West Pomerania (Germany)	Atherosclerosis and MI	Exposed to shift work/unexposed	HR = 1.53 (95% CI 1.06–2.22) of MI at an early age	Age, sex, pack-years smoking
Brown *et al.* [36]	Cohort	F: 28 015 never, 36 400 1–14 years, 3821 15–29 years, 1187 ≥30 years [mean age: 54.5 (never), 55.0 (1–14 years), 56.3 (15–29 years), 60.4 (≥30 years)]	Nurses (USA)	Ischaemic stroke	Rotating night shift work (at least three nights per month in addition to days and evenings in that month) for 1–2, 3–5, 6–9, 10–14, 15–19, 20–29 and ≥30 years/never	HR = 1.04 (95% CI 1.01–1.07) of ischemic stroke per 5 years working rotating night shifts	Age, questionnaire cycle, hypertension, CHD, diabetes, elevated cholesterol, aspirin use, S, AL, PA, BMI, fruit and vegetable intake, menopausal status and use of hormone replacement therapy
Metabolic syndrome							
Karlsson *et al.* [44]	Cross-sectional	F: 4632 shift workers, 9857 day workers; M: 3277 shift workers, 9719 day workers (aged 30, 40, 50, or 60)	General population (Sweden)	Metabolic syndrome (no uniform definition was used; components were defined separately)	Shift work/day work	F: RR = 1.71 ($P < 0.0001$); M: RR = 1.63 ($P < 0.0001$) of having all three components (obesity, hypertension, and high triglycerides)	Age
Sookoian *et al.* [45]	Cross-sectional	M: 474 rotating shift workers, 877 day workers (mean age: 36 rotating shift workers, 34 day workers)	Healthy workers from a factory (Argentina)	Metabolic syndrome (NCEP-ATPIII definition)	Rotating shift work/ day work	OR = 1.51 (95% CI 1.01–2.25)	Age, PA

Table 2. (*Continued*)

Authors	Study design	Population (age)	Population and occupation (Location)	Outcomes	Main exposure/ referents	Main results	Covariates
Esquirol *et al.* [46]	Cross-sectional	M: 100 shift workers; 98 day workers (mean age: 46.54 shift workers; 48.84 day workers)	Workers employed in a chemical plant (France)	Metabolic syndrome (NCEP-ATPIII and IDF definitions)	Rotating shift work (8 h rotating shift: 1 or 2 mornings, 1 or 2 afternoons, 1 or 2 night and 3 or 4 rest days)/day work	OR = 2.38 (95% CI 1.13–4.98) (NCEP-ATPIII); OR = 0.95 (95% CI 0.51–1.78) (IDF)	Age, work organization, total PA, Job Strain Index, S, AL, glucose intake, total energy intake and eating intermediate meals except lunch and dinner
De Bacquer *et al.* [47]	Cohort	M: 1220 day workers, 309 rotating shift workers (35–59 baseline)	Nine different companies and public administrations (Belgium)	Metabolic syndrome (IDF definition)	Rotating shift work/ day work	OR = 1.46 (95% CI 1.04–2.07)	Age, S, PA outside work, education level, job strain, physical job demands; WC, diastolic BP, HDL cholesterol
Pietroiusti *et al.* [48]	Cohort	F: 244 day workers, 278 night workers; M: 92 day workers, 124 night workers (mean age: 38.9 shift workers; 37.9 daytime workers)	Health care workers (Italy)	Metabolic syndrome (updated NCEP definition)	Night shift work or rotating shift work (at least four nights per month during a year)/ daytime work	RR = 5.10 (95% CI 2.15–12.11)	Age, gender, S, AL, WC, family history, sedentariness
Lin *et al.* [49]	Cohort	F: 102 persistent rotating shift workers, 125 persistent day workers (mean age: 32.8)	Workers of an electronic manufacturing company (Taiwan)	Metabolic syndrome (modified NCEP-ATPIII definition)	Persistent rotating shift work/ persistent day work	OR = 3.5 (95% CI 1.3–9.0)	Age, insulin resistance status, metabolic syndrome components, job and lifestyle factors
Lin *et al.* [50]	Cohort	M: 615 persistent rotating shift workers, 381 persistent rotating shift workers: no (mean age: 32.1)	Workers of an electronic manufacturing company (Taiwan)	Metabolic syndrome (modified NCEP-ATPIII definition)	Persistent rotating shift work: yes and e-ALT: yes/ persistent rotating shift work: no and e-ALT: no	OR = 2.7 (95% CI 1.4–5.3)	Age, metabolic syndrome components, insulin resistance, hepatovirus infections, fatty liver, lifestyle and workplace factors
Violanti *et al.* [51]	Cross-sectional	F: 27 day, 7 afternoon, 3 midnight; M: 19 day, 25 afternoon, 17 midnight (mean age: 39.5)	Police officers at a mid-sized urban police department (USA)	Metabolic syndrome (NCEP-ATPIII definition)	Midnight (8:00 pm–3:59 pm)/day (4:00 am–11:59 am)	PR = 1.57 (95% CI 0.41–5.95)	Age, gender, S, AL, education, marital status, police rank and PA
Diabetes							
Mikuni *et al.* [52]	Cross-sectional	M: 1514 shift workers, 653 day workers	Factory labourers (Japan)	Diabetes	Three-shift/day	Prevalence rate of diabetes: 2.1% in three-shift workers; 0.9% in day workers ($P < 0.05$)	N/A
Kawakami *et al.* [53]	Cohort	M: 1015 shift workers, 1179 day workers	Workers at a large electrical company (Japan)	Diabetes	Rotating shift/day	HR = 1.67 (95% CI 0.57–4.90)	Age, education, BMI, S, AL, leisure time PA, and family history
Nagaya *et al.* [54]	Cross-sectional	M: 826 shift workers, 2824 day workers (46.7 ± 7.0 years)	Blue-collar workers attending annual health check-ups (Japan)	Fasting serum glucose ≥7.00mmol/l or patient under treatment for diabetes	Shift work/day work	Age group 30–39 years OR = 6.75 (95% CI 1.31–56.1); age group 40-49 years OR = 1.22 (95% CI 0.68–2.10); age group 50–59 years OR = 0.93 (95% CI0.53–1.55)	BMI, job, S, AL and exercise

Table 2. (*Continued*)

Authors	Study design	Population (age)	Population and occupation (Location)	Outcomes	Main exposure/ referents	Main results	Covariates
Karlsson *et al.* [55]	Cohort	M: 2354 shift workers, 3088 day workers	Workers from two pulp and paper manufacturing plants (Sweden)	Mortality due to diabetes	Shift work (<5 years, 5–9 years, 10–19 years, 20–29 years, ≥30 years)/never worked shifts	Trend per year shift work in mortality due to diabetes as an underlying or contributory cause (*b*(linear coefficient) × 10^{-5} = 4.14, 95% CI 2.46–5.81)	Age
Morikawa *et al.* [56]	Cohort	M: 492 three-shift workers, 228 two-shift workers, 1099 fixed-daytime workers (blue collar); 1041 fixed-daytime workers (white collar)	Blue collar workers in a sash and zipper factory (Japan)	Diabetes	Shift work (two-shift, three-shift)/ fixed day work	RR = 1.73 (95% CI 0.85–3.52) (two-shift versus day workers); RR = 1.33 (95% CI 0.74–2.36) (three-shift versus day workers)	Age, BMI, family history, S, AL, PA
Kroenke *et al.* [57]	Cohort	F: person-years: 106 170 none, 12 670 <12 months, 85 361 1–2 years, 71 167 2–5 years, 42 127 5–10 years, 19 345 ≥10 years (25–42 at baseline)	Nurses (USA)	Type 2 diabetes incidence	Rotating night shift work ≥10 years/ none	Age-adjusted: RR = 1.64 (95% CI 1.11–2.37) Multivariate adjusted (adjusted for BMI): RR = 0.98 (95% CI 0.66–1.45)Multivariate adjusted (not adjusted for BMI): RR = 1.41 (95% CI 0.96–2.06)	Age, family history of diabetes, work hour, job strain, job support, hours at work sitting, hours per week at home, leisure-time PA, S, AL, trans-fat intake, glycaemic load, caffeine intake, marital status, number of children, menopausal status, vitamin supplementation, aspirin use; BMI
Review							
Frost *et al.* [7]	Shift work and ischaemic heart disease: a systematic review			14 Studies were reviewed, of which 7 studied fatal events, 6 combined fatal and non-fatal events and 1 study separated fatal and non-fatal events. Conclusion: 'There is limited epidemiologic evidence for a causal relation between shift work and ischemic heart disease'.[7]			
Boggild and Knutsson [32]	Shift work and CVD: a systematic review			17 Studies were reviewed. Conclusion: '[. . .] the most reasonable risk estimate seems still to be the relative risk of 1.4 derived from the hitherto methodologically most convincing study by Knutsson *et al.* [30] whose results are supported by the demonstration of a dose-response and an equal risk for both genders'.			
Kristensen [31]	Work environment and CVD: a critical review			Included a section of shift work. Conclusion: 'The relative risk of 1.4 found by Knutsson *et al.* [30] is consistent with the results of other studies in the field and must, for the present, be regarded as the most reasonable estimate'.			
Åkerstedt *et al.* [29]	Shift work and CVD: a critical review			The first review on the relationship between shift work and CVD. Conclusion: The up-to-date evidence on the association between shift work and CVD is suggestive of an adverse association.			

AL, alcohol; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; e-ALT, elevated alanine aminotransferase at baseline; F, female; HDL, high-density lipoprotein—cholesterol; M, male; MI, myocardial infarction; N/A, not applicable; PA, physical activity; S, smoking; WC, waist circumference.

[a]Published study descriptions were ambiguous about whether exposures data were originally collected prior to case ascertainment.

of metabolic syndrome have been evolving in the past decade. There are four main definitions, provided by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATPIII), the International Diabetes Federation (IDF), the World Health Organization, and the European Group for the Study of Insulin Resistance

[38–42]. A comprehensive comparison between the different definitions was recently published [43]. Definitions used by the studies reviewed in this paper are also listed in Table 2.

The majority of the published data support an adverse association between shift work and the risk of developing metabolic syndrome (Table 2). The first study on metabolic syndrome found that shift workers were at an increased risk of three metabolic syndrome components (obesity, hypertension, and high triglycerides) compared to day workers, in both women (RR of having all three components = 1.71, $P < 0.0001$) and men (RR of having all three components = 1.63, $P < 0.0001$) [44]. Sookoian *et al.* [45] found a moderately increased risk of metabolic syndrome among rotating shift workers compared to day workers [odds ratio (OR) = 1.51, 95% CI 1.01–2.25]. A study of workers within a petrochemical plant, with 98 strictly rotating shift workers and 100 day workers, found the risk of metabolic syndrome to be more than doubled in rotating shift workers compared to day workers using the definition of NCEP-ATPIII (OR = 2.38, 95% CI 1.13–4.98) but not the definition of IDF (OR = 0.95, 95% CI 0.51–1.78) [46]. A Belgian prospective study reported an increased risk (OR = 1.46, 95% CI 1.04–2.07) of metabolic syndrome in rotating shift workers compared to day workers [47]. Another prospective study focussed on night shift health care workers and reported that working night shifts was associated with a greatly increased risk of metabolic syndrome (HR = 5.10, 95% CI 2.15–12.11) [48]. Lin *et al.* [49] found a significantly increased risk of developing metabolic syndrome in female persistent rotating shift workers compared to persistent day workers (OR = 3.5, 95% CI 1.3–9.0). In a similar study, Lin *et al.* [50] found an increased risk of developing metabolic syndrome in male persistent rotating shift workers, but only among those with elevated serum alanine aminotransferase at baseline (OR = 2.7, 95% CI 1.4–5.3), compared to non-persistent rotating shift workers without elevated serum alanine aminotransferase. In contrast, a study of police officers did not find that those who mainly worked midnight shifts had a higher risk of metabolic syndrome than those who mainly worked day shifts [51]. Because the day shifts started in the early morning (4:00 am) at the research site, this study may not be directly comparable with studies in which the reference group was day shift workers with a more typical daytime work schedule.

Diabetes

Shift work has been hypothesized to be associated with an increased incidence of diabetes; however, evidence from epidemiological studies is limited. An early cross-sectional study of Japanese male factory labourers reported a higher prevalence of diabetes among shift workers than day workers (2.1% versus 0.9%; $P < 0.05$) [52]. More recently, Kawakami *et al.* [53] reported an increased risk of diabetes among rotating shift workers compared to day workers in a small prospective Japanese cohort, but the result was not statistically significant (HR = 1.67, 95% CI 0.57–4.90). In a cross-sectional study of Japanese male blue collar workers, Nagaya *et al.* [54] reported that shift workers were more likely than day workers to have high fasting serum glucose (≥7 mmol/l) or be under treatment for diabetes, for subjects aged 30–39 years (OR = 6.75, 95% CI 1.31–56.1) but not for those aged 40–49 years (OR = 1.22, 95% CI 0.68–2.10) or 50–59 years (OR = 0.93, 95% CI 0.53–1.55). In 2005, Karlsson *et al.* [55] reported that years of shift work in a historical cohort of Swedish pulp and paper industry workers were positively associated with risk of mortality with diabetes as an underlying or contributory cause, although none of the reported results were significant. In a small prospective cohort study of Japanese male factory workers, Morikawa *et al.* [56] found no significant difference in diabetes incidence by shift work; compared to fixed daytime workers, the RR among two-shift workers was 1.73 (95% CI 0.85–3.52) and among three-shift workers was 1.33 (95% CI 0.74–2.36). In the Nurses' Health Study, years of rotating night shifts were found to be positively associated with risk of Type 2 diabetes in an age-adjusted model (RR = 1.64, 95% CI 1.11–2.37 for ≥10 years rotating night shift work versus none) [57]. This association was eliminated in a multivariate adjusted model by additional adjustment for body mass index (RR = 0.98, 95% CI 0.66–1.45).

For metabolic syndrome and diabetes, interpretation of published data is difficult due to a number of issues including ambiguities in information reported on study design, non-comparable shift work patterns, emphasis on non-significant increases in risks or highlighting of positive results from subgroup analyses, insufficient or unclear model adjustments and the absence of a widely accepted definition for metabolic syndrome. For metabolic syndrome, on the basis of mostly statistically significantly positive findings but these methodological limitations, we grade the epidemiological evidence as moderate (RCGP **). For diabetes, based on the fact that there were several studies but only one study reported a statistically significantly elevated risk among shift workers and the issues discussed above, we grade the epidemiological evidence as limited (RCGP *).

Putative mechanisms

Cancer

Night workers are exposed to a variety of factors that may affect the risk of developing cancer. Increased exposure to light at night has been hypothesized to be in part

responsible for the rise in breast cancer incidence seen in the industrialized world [3]. It has been proposed that light at night suppresses the secretion of nocturnal melatonin and there is evidence, predominantly from rodent models [58,59]. This suppressed melatonin production may in turn influence cancer risk through a variety of direct and indirect mechanisms, including alteration of endogenous sex hormone concentrations, an established risk factor for breast cancer [60]. There is some support in the epidemiological literature for the melatonin hypothesis in relation to night work. First, results from some of the studies focussing on the relationship between night work and melatonin production support the hypothesis that night work causes suppression of nocturnal melatonin [61–63]. Second, data from three of the five published prospective studies on the relationship between melatonin and breast cancer are suggestive of a protective effect of higher melatonin levels on breast cancer (see the meta-analysis in Schernhammer *et al.* [64]). The melatonin hypothesis has also been expanded to cancers at sites other than breast cancer [23,25]. There is also growing interest in potential mechanisms operating at the molecular level, including the possible roles of polymorphisms in clock genes and desynchrony of related gene expression in the development of cancer [6]. Results from experimental studies have indicated that clock genes have the potential to influence markers of disease risk including sex hormone concentrations and the functioning of the innate immune system [65,66].

Shift work has also been linked to a range of behavioural and lifestyle factors that may be associated with cancer or modify risks associated with shift work. For example, evidence suggests that shift workers are more likely to be smokers and to have a higher body mass index [13,15,67]. Other studies have shown that shift workers may sleep less and have lower sleep quality than day workers [68,69]. The relationship between sleep duration and cancer risk has been examined in general populations, without regard to work schedules, but the evidence has not been consistent [70–75].

CVD and related chronic conditions

A number of pathways linking shift work to CVD and related chronic conditions have been proposed, including circadian disruption and stress caused by disturbance to normal metabolic and hormonal functions [8,76] and a greater prevalence among shift workers of behaviours, such as smoking and a poor diet, which increase the risk of developing CVD [67]. Circadian disruption caused by shift work has been shown to affect a number of risk factors for developing CVD including blood pressure and blood lipids [47]. It has also been proposed that shift work might result in stress [76]. Neuroendocrine responses to stress involve the increased secretion of glucocorticoids and catecholamines from the adrenal gland and the activation of the sympathetic nervous system [77]. The chronic activation of this stress system may in turn cause suppression of the gonadal, growth hormone and thyroid axes [77]. Such metabolic disturbances may lead to the clinical expression of a number of comorbidities including central obesity, hypertension, dyslipidemia and endothelial dysfunction, all components of the metabolic syndrome and risk factors for CVD [8,76]. As it is for cancer, shift work is associated with a range of lifestyle-related risk factors for CVD and related chronic conditions [7,32].

Box 2. Future research

Future research priorities may include:

- Large prospective cohort studies of shift workers and non-shift workers with multiple, well-characterized disease end points;
- Further data from a wider variety of occupational groups;
- More detailed information on the spectrum of different aspects of shift work, such as duration, frequency, type and pattern;
- Clearer study methodologies for determining whether certain variables, e.g. smoking and BMI, should be treated as confounders or as explanatory factors in the causal pathway in shift work research; and
- More data on proposed mechanisms, such as on the relationships between: melatonin and cancer; sleep and cancer; melatonin and circadian disruption; and clock gene-variants and chronic disease.

Conclusions

This review brings together epidemiological evidence on the relationship between shift work and risk of major chronic diseases, including cancer and CVD. We have identified a number of recent critical reviews of the literature and several subsequent reports containing new data. There is suggestive evidence for an association between night work and increased risk of breast cancer and between shift work and increased risks of CVD (including metabolic syndrome), but limited evidence for an association with cancers at other sites and diabetes. A number of mechanisms may underlie these associations, including those related to suppressed melatonin production and sleep disturbance or deficit, as well as associated lifestyle factors.

The limitations of the published epidemiological data include inadequate characterization of shift work exposure (with respect to pattern, frequency and duration),

a focus on a limited number of occupational groups and shift systems, as well as a limited number of endpoints, and inconsistent or unclear consideration of the role of potential confounders. Notably, there have been few large prospective, population-based investigations of the relationship between shift work and cancer or CVD.

Because evidence for neither cancer nor CVD and other related chronic conditions can be graded as strong (***) using the modified RCGP system, further large-scale prospective studies with detailed exposure data are required to provide more precise quantitative estimates of the impact of shift work on a number of chronic disease endpoints in different groups (e.g. men and women, and in specific age groups), to examine putative mechanisms and to tease out the importance of lifestyle factors as mediators of the association or as potential confounders (Box 2). The findings from the reports reviewed here and from future epidemiological investigations should ultimately inform employment guidelines and public health interventions aimed at reducing risks among shift workers.

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Conflicts of interest

None declared.

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