Original article

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Associations between shift work and use of prescribed medications for the treatment of hypertension, diabetes, and dyslipidemia: a prospective cohort study

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Objective This study examined the associations between shift work and use of antihypertensive, lipid-lowering, and antidiabetic medications.

Methods Survey data from two cohorts of Finnish men (N=11 998) and women (N=49 944) working in multiple occupations where shift work was used were linked to national Drug Prescription Register data, with up to 11 years of follow-up. In each cohort, age-stratified Cox proportional hazard regression models were computed to examine any incident use of prescription medication for each of the three medical conditions, separately comparing each of two groups of rotating shift workers (those whose schedules included night shifts, and those whose schedules did not include night shifts) with day workers who worked in a similar range of occupations.

Results In the larger cohort, among participants aged 40–49 at baseline, shift work without night shifts was associated with increased use of type-2 diabetes medication after adjustments for sex, occupational status, marital status, alcohol consumption, smoking, and physical activity [hazard ratio (HR) 1.28, 95% confidence interval (CI) 1.01–1.62], while shift work with night shifts was associated with increased use of dyslipidemia medication after adjustments (HR 1.33, 95% CI 1.12–1.57). There were no such associations among younger and older shift workers. Also in the larger cohort, among those aged <50 years at baseline, both types of shift work were associated with increased use of hypertension medication after adjustments [up to HR 1.20 (95% CI 1.05–1.37)]. There were no positive associations in the smaller cohort.

Conclusions There was mixed evidence regarding the use of medications for cardiovascular risk factors by shift workers. Selection effects may have affected the associations.

Key terms cardiovascular disease; coronary heart disease; CVD; drug register; night shift; night work; rotating shift; shift worker.

Shift workers are exposed to higher levels of physiological stress than their day-working counterparts due, at least in part, to chronic exposure to circadian disruption. This may increase shift workers' susceptibility to cardiovascular risk factors, such as hypertension, atherosclerosis, and type 2 diabetes (1). However, while some studies have identified associations between exposure to shift work and such medical conditions, the overall picture is of a mixed set of findings.

Many studies (eg, as reviewed by 2–6) have variously suffered from being based on relatively small samples or samples drawn from restricted populations (eg, from a single organization or single sex); using cross-sectional designs; including only limited adjustment for potential confounds; relying on self-reported indices of disease; and using quite vague or non-specific definitions of shift work. Thus there is a risk that such studies were statistically underpowered, lacking gen-

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eralizability, lacking the temporal element needed to established causality, subject to selection biases (eg, the "healthy shift worker effect"; 7) or subject to outcome misclassification. Furthermore, the effects of shift work may have been diluted by a failure to distinguish between more and less harmful shift schedules (ie, those engendering more or less circadian disruption; 8).

An important element of ascertaining links between shift work and disease is the use of reliable indices of the presence of disease. In previous studies, objective assessments of health status were most commonly derived from physical examinations (eg, blood pressure measurements or blood sampling, taken as part of a medical check-up; 2, 3). Collection of such data is labor intensive. Hence many of the studies of this type were based on relatively small samples or samples from restricted populations (eg, the employees of a single organization; 9, 10). Another less commonly used objective index of disease status is the administrative records of medication prescriptions / purchases. The use of medication is in most cases likely to correspond closely with the medical diagnosis of a disease. Moreover, where medication prescription / purchase records are available nationally (as in national register data that is collected in Scandinavian countries), it affords the possibility to examine associations within a broad sample of the population. We are aware of only one published study to date that used data from national registers of prescribed medication purchases to examine associations between shift work and any of the diseases that are the focus of the current study (11). This study found no association between shift work status and the purchase of hypertension medication, although the study suffered from using a broad definition of shift work.

To address the methodological issues outlined above, the current study sought to examine prospectively the potential associations between specific forms of shift work and objective indices of disease, in two large national surveys of male and female workers in a range of occupations, comparing shift workers with day workers in the same range of occupations. The survey data were linked to national register data on the purchase of medications for the treatment of (i) hypertension or high blood pressure (ii); type 2 diabetes; and (iii) dyslipidemia (a commonly studied biomarker of atherosclerosis). The surveys included detailed questions on a broad range of background characteristics and work schedules, thus facilitating the separate study of rotating shift schedules that either did, or did not, involve nightwork. It also made it possible to account for a range of potential confounders that could distort findings, such as health behaviors and previous shift work history. In order to address the issue of selection effects, the analyses were stratified by age, as selection out of shift work due to the development of ill-health is most likely to occur among older shift workers.

It was hypothesized that shift work would be associated with greater use of each type of medication, after adjusting for potential confounders relating to demographic and economic background, and health behaviors. It was further anticipated that these effects would be greater for shift work that included night work than for shift work that did not, due to the greater level of circadian disruption that is caused by night work.

Method

Participants

Data were obtained from three waves of the Finnish Public Sector (FPS) study (2000, 2004, and 2008, response rates 66–68%). The FPS comprised two cohorts: the 10-town cohort, a study of local government employees in ten towns (a mixture of healthcare workers – mainly in residential long-term care settings – and enemployees from other occupational sectors) and the Work and Health in Finnish Hospital Personnel Study, a study conducted within 21 hospitals, referred to here as the hospitals cohort. The total number of participants in the two cohorts before exclusions (see below) was N=59 199 and N=27 364, respectively.

Participants entered the study at different points (ie, either 2000, 2004, or 2008), depending on their work schedule status at the time they first responded to the survey. The follow-up for purchases of prescribed medication began from the start of the year following the survey. Respondents classified as day workers were excluded if their occupation did not match the occupation of at least one of the participants classified as shift workers (see below); this resulted in the exclusion of 3.6% of the original sample of day workers. For each analysis, we excluded respondents who had purchased the medication in question during the 12 months preceding follow-up and those who reported at baseline ever having been diagnosed by a doctor with either hypertension, myocardial infarction, angina pectoris, stroke/cerebrovascular disease or diabetes. For the analysis of each model, participants with incomplete baseline data for the relevant covariates were excluded.

Shift work status

For the purposes of the current analyses, participants were classified as either day workers, shift workers without night shifts or shift workers with night shifts. Classification was based on their survey response at baseline.

In the 10-town cohort, participants in the 2000 and 2004 waves were asked: "Is your work regular day work?", with the response options "Yes" or "No". If

answering in the negative, they were then asked to indicate if their work included (i) evening (ii), night, or (iii) weekend shifts. Participants were classified as day workers if they answered "Yes" to the initial question; as shift workers without night shifts if they answered "No" to the initial question and then indicated that their work included evening shifts but not night shifts; or as shift workers with night shifts if they answered "No" to the initial question and then indicated that their work included both evening shifts and night shifts. Participants selecting any other combination of responses were excluded from the analyses (N=1062).

In the Hospitals Cohort and the 2008 wave of the 10-town cohort, participants were classified according to whether they chose to describe their current work as either day work, shift work without night shifts, or shift work with night shifts. These questionnaire items have previously been validated against an objective measure of shift work status based on payroll data (12). Participants who reported regular night work or other irregular work / other were excluded from the analyses (N=1786).

Use of prescription medicine

Data on the dates of purchases of prescription medication were retrieved from the Drug Reimbursement Register from 1 January 1999 to 31 December 2011. The analyses focused on specific medications related to three medical conditions, based on the anatomical therapeutic chemical (ATC) classification system. The three categories were: type-2 diabetes (A10B, A10X); hypertension (C02, C03, C07, C08, C09); and dyslipidemia (C10AA, ie, statins). The date of the first purchased prescription was used to determine the occurrence of the medical condition.

Covariates

Covariates measured at baseline included sex, occupational status [four categories: upper white-collar (International Standard Classification of Occupations - ISCO=1-2), lower white-collar (ISCO=3-4), skilled blue-collar (ISCO=5), other blue-collar (ISCO=6-9), marital status (four categories: unmarried, married or cohabiting, divorced, widower), alcohol consumption (continuous measure: pure alcohol g/week), current smoking status (two categories: no, yes), physical activity (continuous measure: metabolic equivalent (MET) hours/week) and body mass index (BMI, continuous measure: kg/m^2)]. All baseline data were obtained from the survey responses.

Data analysis

Participants' survey responses were linked to data on redeemed prescriptions and death obtained from the national registers using personal identification numbers and the linkage was successful for all respondents.

Associations between shift work status and any incident use of studied prescription medicine were examined using Cox proportional hazard regression models. Given that the two cohorts featured different exposure assessments (see above) and also that the two cohorts worked in different occupational settings (and thus may differ with respect to, for example, shift patterns, or the distribution of work tasks between shift workers and non-shift workers), initially it was decided to analyze data from the two cohorts separately. The intention was to ascertain whether the associations between shift work status and medication use differed between the two cohorts, and if they did not, the two datasets would be combined into a single set of analyses. The results indicated that there were rather large differences and so the decision was taken to keep the two datasets separate. For each cohort, two sets of analyses were conducted separately for each of the three types of medication, one comparing shift workers without night shifts with day workers and the other comparing shift workers with night shifts with day workers. In order to test the Cox proportional hazard assumptions, the time-independent interaction between shift work groups and the follow-up period were examined and found to be statistically non-significant (results not shown), confirming that the proportional hazards assumption was justified (13).

Follow-up for day workers began from the beginning of the first year (1 January) after they responded to the survey. Follow-up of shift workers with / without night shifts began from the beginning of the first year after they indicated that they were doing shift work with / without night shifts. Follow up time was calculated to the first date of purchase of medication, death or end of the follow up (ie, 31 December 2011), which ever came first. Each analysis was stratified by age at baseline (≤39, 40–49, and ≥50 years). We calculated hazard ratios (HR) and their 95% confidence intervals (CI) without adjustments (model 0); with adjustments for sex, occupational status and marital status (model 1); with adjustments in model 1 plus adjustments for alcohol consumption, smoking and physical activity (model 2); and with adjustments in models 1 and 2 plus BMI (model 3). This multiple-model approach was adopted in view of the potential role of some of the covariates as mediators of the associations under study. Alcohol consumption, smoking, physical activity, and especially BMI are all potential mediators of the outcomes and therefore their inclusion risked masking associations through over-adjustment. In order to account for the non-Gaussian distributions of the variables measuring alcohol consumption, physical activity, and BMI, these variables were entered along with their squared terms.

Sensitivity analyses were conducted to investigate the possibility that having former shift workers in the control groups could produce an under-estimation of the true impact of shift work. These analyses were only possible in the hospital cohort, where shift work history was reported. The sensitivity analyses involved repeating the main analyses (as described above), but with the modification that day workers were excluded from the control group if they reported having previously worked shifts for more than one year. The results were compared with those of the main analyses to see whether these supplementary analyses produced stronger effects than the main analyses. If they did, this would be taken as an indication that the main analyses underestimated the true impact of shift work, due to the 'contamination' of the control sample by former shift workers.

The statistical analyses were conducted with SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Ethical approval

The ethics committee of the Hospital District of Helsinki and Uusimaa (HUS) approved the FPS study (HUS 1210/2016).

Results

The mean follow-up times were 8.1 years for the analyses of type 2 diabetes, 7.2 years for hypertension and 7.8 years for dysplidemia. Table 1 shows the number of participants included for each of the three types of medication examined, as well as sex distributions and mean ages. As also shown in the table, the samples did not differ substantially from the full study sample with respect to sex distribution or mean age.

Descriptive statistics of the final samples for each cohort, broken down by work schedule, are presented in tables 2a and b. Age distributions were similar between day workers and shift workers without night shifts, but there were higher proportions of younger (≤39 years) shift workers with night shifts. Sex distributions were broadly similar across the three types of work schedule, with the majority of both day and shift workers being female. The distributions of occupational status differed between the three types of work schedule, with the majority of day workers being in the upper two strata, shift workers without night shifts being relatively evenly spread between the four strata, and the majority of shift workers with nights being in the middle two strata. The distributions of marital status did not differ between the three types of work schedule, with the majority in each cohort being married or cohabiting. Shift workers (both types) were somewhat more likely to be smokers but tended to consume less alcohol (with the exception of shift workers with nights in the 10-town cohort), while levels of physical activity and BMI were quite similar across the three types of work schedule.

Table 1. Baseline profiles: full study sample and samples included in analyses of each medication after exclusions. [SD=standard deviation.]

	10-town cohort		Hospital cohort	
	N (% female)	Baseline mean age (SD)	N (% female)	Mean age (SD)
Full study sample	42 846 (79.0)	43.8 (9.8)	24 046 (87.6)	42.5 (10.2)
Samples included after exclusions				
Type-2 diabetes	38 209 (79.1)	43.0 (9.7)	21 762 (87.6)	42.3 (10.7)
Hypertension	34 583 (79.5)	42.2 (9.6)	19 892 (87.6)	41.5 (10.1)
Dyslipidemia	38 243 (79.2)	44.0 (9.7)	21 631 (87.6)	42.2 (10.1)

Table 3 presents the observed cumulative incident proportions for the three medications, broken down by shift work status and age (a full breakdown of cumulative incident proportions broken down by all predictors and background variable categories is provided in supplementary table S1, www.sjweh.fi/show_abstract.php?abstract_id=3813). For all three types of medication, any incident use tended to be highest among shift workers without night shifts and older individuals. Supplementary table S2 (www.sjweh.fi/show_abstract.php?abstract_id=3813) presents the numbers of participants, events and person-years, stratified in accordance with main analyses.

Table 4 presents the results from the Cox regression analyses of associations between shift work status and any incident use of each of the three categories of medicine. (Note that the table only presents the results for models 1 and 2; see *Data analysis* above. Results for models 0 and 3 are presented in supplementary table S3, www.sjweh.fi/show_abstract.php?abstract_id=3813). Results from the 10-town cohort indicated several significant associations between work schedule and medication use, all of which were positive. There were positive associations between shift work (both types) and any incident use of hypertension medication in both the lower and middle age ranges (≤39 and 40–49 years) after adjustment for sex, occupational status, marital status, alcohol consumption, smoking, and physical activity (model 2). There were additional positive crude associations between shift work without night shifts and any incident use of diabetes medication in the middle age ranges after adjustments (models 1 and 2). Finally, there were positive associations between shift work with night shifts and any incident use of dyslipidemia medication in the middle age range after adjustments (models 1 and 2).

By contrast, in the hospital cohort, there were no significant positive associations between work schedule and medication use, but there were some negative associations (ie, indicating shift workers were less likely

Table 2a. Baseline descriptive statistics of final sample in each cohort, broken down by work schedule.

	10-town cohort						Hospital cohort					
	Day work		Shift work without night shifts		Shift work with night shifts		Day work		Shift work without night shifts		Shift work with night shifts	
	N	%	N	%	N	%	N	%	N	%	N	%
Age at baseline												
≤39	11 100	34	1994	31	1739	43	3519	31	1257	32	4523	52
40-49	10 744	33	2154	33	1275	32	3943	35	1139	29	2645	30
≥50	10 547	33	2307	36	986	25	3881	34	1510	39	1619	18
Sex												
Male	6786	21	955	15	1269	32	1939	17	238	6	811	9
Female	25 605	79	5500	85	2731	68	9414	83	3668	94	7976	91
Occupational status												
Upper white-collar	14 409	45	1147	18	212	5	3834	34	309	8	65	1
Lower white-collar	7065	22	1610	25	1115	29	5588	49	1533	39	6496	74
Skilled blue-collar	6263	19	2428	38	2359	59	728	6	522	13	2063	23
Other blue-collar	4654	14	1270	20	314	8	1203	11	1542	40	163	2
Marital status												
Unmarried	3742	12	930	15	584	15	1148	10	511	13	1363	16
Married / cohabiting	24 482	77	4400	69	2850	72	8828	79	2788	72	6512	75
Divorced	3393	11	890	14	473	12	1114	10	491	13	767	9
Widow(er)	384	1	123	2	42	1	152	1	80	2	80	1
Smoking status												
No	25 991	82	4793	77	2844	74	9394	88	2940	81	6885	84
Yes	5604	18	1463	23	1013	26	1221	12	711	19	1298	16

Table 2b. Baseline statistics of final sample in each cohort, broken down by work schedule. [BMI=body mass index; MET=metabolic equivalent SD=standard deviation; wk=week.]

	10-town cohort						Hospital cohort					
	Day work		Shift work without night shifts		Shift work with night shifts		Day work		Shift work without night shifts		Shift work with night shifts	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Alcohol consumption (g/wk)	68.0	103.8	59.1	97.2	75.2	130.9	56.8	88.9	47.1	98.2	46.4	80.3
Physical activity (MET hours/wk)	4.57	4.1	4.5	4.2	5.37	4.9	4.6	4.0	4.6	4.3	5.3	4.6
BMI (kq/m^2)	25.1	4.3	25.5	4.5	25.9	4.4	24.8	4.6	25.2	4.1	24.6	4.0

Table 3. Sample size and frequency of any-incident use of medication, broken down by shift work status and age at baseline.

	Medication					
	Type-2 diabetes		Hypertension		Dyslipidemia	
	N	% new redemptions	N	% new redemptions	N	% new redemptions
10-town cohort						
Shift work status						
Day work	28 947	3.8	26 202	20.6	28 975	12.1
Shift work without night shifts	5653	4.6	5072	24.2	5658	13.3
Shift work with night shifts	3609	3.5	3309	21.2	3610	12.2
Age at baseline						
≤39	14 056	1.6	13 784	12.8	14 150	3.1
40–49	12 868	3.8	11 726	23.7	12 942	12.3
≥50	11 285	6.9	9073	30.7	11 151	23.8
Hospital cohort						
Shift work status						
Day work	10 215	3.7	9225	25.4	10 139	12.9
Shift work without night shifts	3512	4.0	3121	26.7	3505	13.8
Shift work with night shifts	8035	2.8	7546	21.9	7987	8.4
Age at baseline						
≤39	8564	1.9	8438	15.9	8598	2.4
40–49	7051	2.8	6497	28.5	7035	11.5
≥50	6147	6.2	4957	33.1	5998	24.0

Table 4. Associations between shift work without night shifts and shift work with night shifts and any incident use of medication.

	Model	10-town cohort, age at baseline						Hospital cohort, age at baseline					
		≤39 years		40–49 years		≥50 years		≤39 years		40–49 years		≥50 years	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Hypertension													
Shift work without	1 [a]	**1.22**	**1.07–1.39**	**1.13**	**1.02–1.25**	1.05	0.94–1.16	1.10	0.92–1.30	1.04	0.91–1.20	1.06	0.93–1.21
night shifts	2 [b]	**1.20**	**1.05–1.37**	**1.16**	**1.04–1.29**	1.05	0.95–1.17	1.11	0.93–1.33	1.06	0.92–1.22	1.04	0.91–1.20
Shift work with	1 [a]	1.14	0.98–1.33	1.13	0.99–1.30	1.06	0.91–1.23	0.89	0.77–1.02	**0.88**	**0.78–0.99**	0.95	0.82–1.09
night shifts	2 [b]	**1.18**	**1.00–1.38**	**1.16**	**1.01–1.33**	1.05	0.90–1.22	0.91	0.79–1.04	0.90	0.80–1.02	0.95	0.82–1.09
Type-2 diabetes													
Shift work without	1 [a]	1.23	0.87–1.73	**1.28**	**1.01–1.62**	0.91	0.74–1.11	1.05	0.63–1.74	1.33	0.88–2.02	0.83	0.63–1.10
night shifts	2 [b]	1.24	0.87–1.75	**1.28**	**1.01–1.62**	0.87	0.70–1.08	0.92	0.54–1.55	1.28	0.84–1.94	0.84	0.63–1.12
Shift work with	1 [a]	1.03	0.67–1.59	0.93	0.66–1.29	0.93	0.70–1.24	1.04	0.70–1.54	1.24	0.86–1.79	0.78	0.57–1.07
night shifts	2 [b]	1.06	0.68–1.66	0.90	0.64–1.28	0.93	0.69–1.25	1.09	0.74–1.63	1.30	0.91–1.88	0.79	0.57–1.09
Dyslipidemia													
Shift work without	1 [a]	1.23	0.95–1.59	1.02	0.89–1.18	1.04	0.93–1.16	1.19	0.78–1.81	1.21	0.98–1.48	1.02	0.88–1.18
night shifts	2 [b]	1.19	0.91–1.56	1.03	0.90–1.19	1.04	0.94–1.17	1.12	0.73–1.73	1.21	0.98–1.50	1.03	0.89–1.20
Shift work with	1 [a]	1.09	0.81–1.47	**1.26**	**1.07–1.49**	1.01	0.86–1.18	0.94	0.64–1.38	1.03	0.86–1.23	**0.81**	**0.69–0.94**
night shifts	2 [b]	1.17	0.87–1.59	**1.33**	**1.12–1.57**	1.00	0.85–1.17	0.94	0.63–1.37	1.07	0.89–1.28	**0.81**	**0.69–0.95**

[a] Adjusted for sex, occupational status, and marital status.

[b] Model 1 + alcohol consumption, (alcohol consumption)^2, smoking, physical activity, and (physical activity)^2. Results for Models 0 and 3 are presented in the online supplementary material (see text). **Significant associations in bold.**

than day workers to use medication). Shift workers with night shifts who were in the middle age range showed a lower risk for purchasing hypertension medication after adjustment for sex, occupational status, and marital status (model 1), although the association disappeared after additional adjustment for alcohol consumption, smoking and physical activity (model 2). There were also negative associations between shift work with night shifts and any incident use of dyslipidemia medication in the middle age range medication after adjustments (models 1 and 2).

In the sensitivity analyses of the data from the hospital cohort, we found that excluding day workers who reported having previously worked >12 months in shift work made very little difference to the pattern of results obtained (results not shown).

Discussion

The results of this large prospective cohort study with linked prescription data and a follow-up of 11 years provided mixed evidence of associations between shift work and incident use of medications for type-2 diabetes, dyslipidemia, and hypertension. In the larger of the two cohorts, shift work was associated with greater use of medications for diabetes and dyslipidemia among the 40–49-year-old employees but not among the younger or older workers. Shift work was also associated with greater use of antihypertensive medication among workers <50 years. The smaller cohort, however, provided no evidence of positive associations between shift work and medication use.

The finding of associations between shift work and type-2 diabetes in the 10-town cohort is consistent with previous research, as reflected in the findings of two recent meta-analyses (5, 6). Unexpectedly, however, we found risk to be greater among shift workers without night shifts than among shift workers with night shifts. This was somewhat surprising given that the increased risk of diabetes among shift workers is thought to be linked to circadian disruption and sleep deprivation, which tend to be greater among those whose schedule includes night shifts. The finding may reflect selection out of night work into shift work without nights, as was observed in another recent study based on the FPS study (14). In that study, a lack of association between night work and common mental disorders (CMD) was found to be mainly attributable to the greater likelihood of night workers with CMD moving back to non-night work. (In most cases it is likely to be easier organize a transfer from shift work with nights to shift work without nights, rather than a transfer to day work.) Such selection processes are the likely effect of occupational health practice in Finland which is based on the EU working hours directive (2003/88/EC). This requires that night workers suffering from health problems such as diabetes should be transferred to non-night work whenever possible. Such practices may differ between settings and between countries (eg, between countries that are within the EU and those that are outside the EU). This may go some way to explaining the contrasting findings between studies with regard to the relative risks associated with shift work that either does or does not include night work.

Previous research has produced mixed findings regarding a possible risk of increased cholesterol levels among

shift workers, although an earlier review concluded that there was little evidence of an association (3). The current finding of greater use of medication for dyslipidemia (ie, mainly statins) by shift workers with night shifts in the middle age range might be seen as lending support to a link between shift work and dyslipidemia. However, interpretation of these particular results is complicated by the fact that statins are sometimes prescribed to CVD patients (or potential patients) in the absence of direct evidence of dyslipidemia (15). Thus, we cannot be sure whether the current finding demonstrates a link between shift work and dyslipidemia or between shift work and some other disease(s) for which statins may sometimes be prescribed (eg, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis).

Some of the crude associations between shift work and use of medications were weakened after controlling for individual differences and situational factors (sex, occupational status, and marital status; model 1. See supplementary table S3). Additional controlling for lifestyle factors (alcohol consumption, smoking, physical activity (model 2) and for BMI (model 3) had little clear and systematic effect on the strengths of associations across the entire set of analyses. Nevertheless, there were some instances where the associations between work schedule and use of medications for diabetes and dyslipidemia became weaker after controlling for body mass index. Obesity is strong risk factor for type-2 diabetes (16) and hyperlipidemia (17). Since shift work and sleep deprivation increase appetite, weight gain, and obesity over time (18), controlling for obesity in the current analyses probably lead to an underestimation of the associations between shift work and diabetes and between shift work and dyspidemia.

The finding of associations between shift work and use of hypertension medication is consistent with findings from several other longitudinal studies that have suggested a link between shift work and hypertension symptomatology, based on measurements of blood pressure, self-reports of treatment for hypertension, or records of medical insurance claims (3, 9, 10, 19–20). In the current study, both forms of shift work (with and without nights) were associated with greater use of antihypertensive medication. This contradicted our prediction that risk of disease would be higher for shift work with nights due to greater circadian disruption. Given that both categories of shift worker in the current study worked evening shifts as part of their rotating schedule, our findings might suggest that it is exposure to evening shifts that leads to increased use of antihypertensive medication. Evening shifts are unlikely to be especially disruptive to circadian rhythms, but they may cause other problems that increase the risk of hypertension. For example, evening shifts can be especially disruptive to social and family life; moreover, the late finishing times of evening shifts may cause problems for unwinding and falling asleep (21). Epidemiological studies suggest that hypertension is associated with short sleep (22–24). Another possibility is that some night workers suffering from high blood pressure have been transferred to non-night work whenever possible.

In contrast to the previous findings of associations between shift work and hypertension symptomatology (3, 9, 10, 19), the only previous study of links between shift work and hypertension medication purchase (based on objective register data) found no significant association (11). Both that study and the current study were prospective cohort studies, based on large samples of the Finnish population, adjusting for a similar range of potential confounders. The authors of the earlier study conceded that their use of an imprecise definition of shift work might have attenuated any associations with the outcome variable. While the current study used rather more specific definitions of shift work, it is plausible that the discrepancy between the significant findings in the 10-town cohort, and the non-significant findings in both the hospital cohort and the previous study by Hublin et al (11), may be due to unmeasured differences in the precise nature of the shift schedules (eg, the regularity of the shift patterns or the intensity of nightwork).

The current findings of associations between shift work status and use of antihypertensive medication should be interpreted cautiously as some of these drugs are used to treat common symptoms and conditions such as (premenstrual) oedema and migraine. Thus, they should be regarded as consistent with, rather demonstrative of, a link between shift work and hypertension.

The majority of significant associations (after adjustment for confounders) were observed in the middle age groups. It could be expected that medication would tend to be greater among middle-aged than younger workers, given that any negative effects of shift work on health will develop over a prolonged period. Thus, for example, Pan et al (25) reported a dose–response relationship between shift work exposure and risk of developing type-2 diabetes, such that every five years exposure to rotating night shifts was associated with a 5% increased risk. Dose–response relationships have also been observed between shift work exposure and other related health complaints such as metabolic syndrome (26) and cardiovascular heart disease (27). Such an effect of accumulated shift work exposure would account for the greater number of significant associations among the middle-aged groups in the current study, as compared to the younger-aged groups.

Dose–response relationships are, however, inconsistent with the relatively low (and mostly non-significant) risks observed among the oldest age groups. And yet, it is not uncommon for associations between shift work and health to be less strong, or even absent, in the

groups with the greatest exposure due to strong selection effects that are often observed in shift work research. For example, in the classic study of the association between shift work and ischemic heart disease by Knutsson and colleagues (28), risk was increased among those with 11–15 years of exposure and further increased among those with 16–20 years exposure, but then risk fell sharply after 20 years of shift work. This decrease in risk was attributed to selection effects ("the healthy shift worker effect"), whereby only the healthiest and most resilient individuals remain in shift work after such a long period of exposure (29). EU legislation requires regular health checks for shift workers and that workers be transferred to day work when health problems are identified, a practice that is common in Finland. Thus, the lack of effects in the older age group in the current study may well reflect such selection processes. Another factor to consider is that old age is associated with the accumulation of competing risk factors, thereby diminishing the relative role of shift work compared to these other factors.

Shift work had largely neutral or even negative (ie, protective) effects in the hospital cohort, while positive (ie, harmful) effects were more prevalent in the 10-town cohort. The hospital cohort featured a substantially smaller sample and therefore had lower statistical power. This could account for the relative lack of positive effects but would not explain the presence of negative effects. The results of sensitivity analyses provide no evidence that the control sample in the hospital cohort was 'contaminated' by prior exposure to shift work, which could have produced a left truncation bias (30). This suggests that the effects of shift work were not underestimated in the hospital cohort due to the control sample including individuals whose health had been negatively affected by previous exposure to shift work (ie, bias in selection out of shift work; the 'healthy shift worker survival effect'). Another more likely explanation for the discrepant results, as noted above, is that the current analyses do not take into account the precise nature of the shift schedules. It has been shown previously that introducing more ergonomic shift schedules can, for example, produce positive changes in cholesterol levels (31). It may be that at least some shift workers in the 10-town cohort had more demanding schedules that, for example, promoted greater levels of circadian disruption, as compared to shift workers in the hospital cohort.

The strengths of the current study were that it examines three major health outcomes in a prospective cohort design based on two large employee cohorts with high participation rates linked to high quality national prescription register data. Prospective designs are subject to less risk of error due to confounding or bias compared to retrospective designs (32). The use of register data removes subjectivity, and its associated potential inaccuracies and bias, from the assessment of the participants' state of health. The detailed survey data facilitated adjustment for a broad range of potential confounders. The measure of shift work status that was used in the hospital cohort and in the 2008 wave of the 10-town cohort has been validated against an objective measure based on payroll data (12). The risk of major selection bias was reduced by recruiting all cases and their controls from the same cohort.

As noted above, interpretation of the study is limited by the lack of more detailed information regarding the shift patterns that were worked. Moreover, shift working status (past and present) was assessed through self-reports, as were the majority of other measures included in the analyses. While self-reports of shift working status in this population have been shown to be reliable for day work and shift work with night shifts, they are less reliable for shift work without nights (8). This could have led to misclassification and an underestimation of health effects associated with shift work without nights. Neither of the current analyses took into account possible changes in the participants' shift work status during follow up, which also increases the possibility of misclassification of work schedule.

The potential impact of selection bias *out of* shift work (ie, the 'healthy shift worker survival effect') was examined in the sensitivity analyses of the hospital cohort data. However, no information was available on the shift work history of participants in the 10-town cohort, thereby limiting the possibilities for determining whether those results could have been affected by day workers in the control group having previously worked shifts. Moreover, the possibility of selection bias *into* shift work (ie, the 'healthy shift worker hire effect') remains in both cohorts, as the control groups could have included individuals who had chosen to avoid ever entering shift work due to pre-existing medical conditions or poor health. Such selection bias could lead to an underestimate of health effects.

The current study examined work schedule as a predictor of time to first incident use of medication, rather than the quantity of medication purchased or the duration of its use. Focusing on time to first incident use gives the most precise assessment of the association between the timing of exposure and the manifestation of the related medical condition. However, it also means that the analyses do not take into account the severity of the diagnosed condition or for how long treatment continued. More generally, there are methodological issues to consider around using medication purchase data as a proxy for medical diagnosis. There is no one-to-one correspondence between the prescription of a medication and a particular indication. A particular type of medication may be prescribed for a range of possible indications (as noted above in relation to statins

and antihypertensive medications); and there may be a range of medications that are prescribed for a particular indication. Illnesses may go undiagnosed or may be misdiagnosed, such that the sufferer is not prescribed the appropriate treatment. For type-2 diabetes, dyslipidemia, and hypertension, the estimated prevalences of undiagnosed conditions are relatively high, ranging between 7–38% (33, 34). Finally, there will have been a short interval between survey response (which took place in late autumn) and commencement of follow-up (the beginning of the next year) during which time the outcome (ie, recorded purchase of medication) could not occur – so called 'immortal time' (32). Such biases could not explain the observed differences in rates of medication use between the day and shift workers; however, they give us reason to be cautious when extrapolating from rates of medication use to prevalence of disease.

Finally, while the 10-town cohort comprised employees from a range of occupational sectors, the overall sample was nevertheless dominated by healthcare workers and thus cannot be considered representative of all occupational sectors that employ shift workers.

In conclusion, the current findings provide mixed evidence regarding the use by shift workers of medications for type-2 diabetes, dyslipidemia, and hypertension, conditions that are well-known cardiovascular risk factors. It is possible that selection into and out of shift work may have affected the results, attenuating the observed associations. Future research on shift work and cardiovascular health should use more detailed information on participants' current and previous working time arrangements, ideally in the form of objective working time records.

Conflicts of interest

The authors declare no conflicts of interest.

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