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Night shift work characteristics and risk of incident coronary heart disease among health care workers: national cohort study

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Abstract

Background: Night work has been associated with coronary heart disease. The present study examined exposure-response relations between quantitative night work characteristics and coronary heart disease (angina pectoris or myocardial infarction) with the aim to contribute to evidence-based recommendations for low-risk night work schedules.

Methods: We followed 100 149 night workers (80% women) and 153 882 day workers (78% women), all health care workers in Denmark with day by day payroll information on night shifts from 2007 to 2015. We analysed data with Poisson regression stratified by sex and adjusted for age, calendar year, diabetes, family history of cardiovascular disease, educational level, occupation, indicators for obesity, hypercholesterolaemia, and hypertension.

Results: Female and male night workers worked on average 1.7 and 1.8 night shifts per month for an average duration of less than 4 years. During follow-up, 1198 night and 2128 day workers were hospitalized with first-time coronary heart disease. When compared with day workers, the overall incidence rate ratios for female and male night workers were 1.06 [95% confidence interval (CI): 0.97, 1.17] and 1.22 (95% CI 1.07, 1.39). Highest risks were observed in top exposure categories for several night work characteristics. However, no consistent exposure-response relations by number of monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shift and consecutive night shifts were observed among the night workers of either sex.

Conclusions: This study of a population with low exposure to night work does not indicate that reducing extent of monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shift and consecutive night shifts would reduce the risk of coronary heart disease.

Keywords: Angina pectoris, myocardial infarction, occupation, follow-up study, shift work.

Key Messages

- Men, but not women, with low-level night work as recorded day by day since 2007, showed a 20% increased risk of coronary heart disease. Highest risks were observed in top exposure categories for several night work characteristics.
- The risk of coronary heart disease did not increase in an exposure-response manner with increasing number of monthly, cumulative or consecutive night shifts, years with rotating night shifts or years with any night shifts, indicating that reducing extent of night work according to these characteristics would not reduce the risk of coronary heart disease in low-exposed populations such as in the current study.

Introduction

In 2016, the American Nurses' Health Study showed increasing risk of coronary heart disease with increasing years of rotating night shift work.[1] This observation supports a causal association and is the pinnacle of repeated epidemiological evidence of increased risk of cardiovascular diseases following night and other shift work.[2–6] The existing literature of more than 40 studies has relied on self-reported or company employment information on shift work, with few details of night work characteristics.[3–5] This limits evidence-based recommendations for low-risk night work schedules.[6] Such recommendations are needed because night work is widespread and vital societal institutions depend on work outside standard day working hours.[7]

Based on day by day information on starting and ending time of every shift, obtained from payroll data, we analysed coronary heart disease risk following several quantitative night work characteristics, with the aim to contribute to evidence-based recommendations for night work schedules.[8]

Methods

We conducted a register-based nationwide cohort study with follow-up from 2007 to 2015.

Population

From the Danish Working Hour Database of all public hospital workers in Denmark, we identified 261 415 physicians, nurses, auxiliary nurses, janitors, orderlies and other less or higher skilled occupations with at least one work shift of ≥ 3 h between 1 January 2007 (four hospital regions) or 2008 (one hospital region) and 3 December 2015.[9] We excluded 2738 workers diagnosed with coronary heart disease, as defined later, before start of follow-up and 4646 workers with no data on occupation or educational level.

Coronary heart disease

We defined incident coronary heart disease as the first registration of angina pectoris or myocardial infarction in the National Patient Register that classifies all contacts at all hospitals in Denmark by diagnosis (inpatients 1977–2015, outpatients 1994–2015), supplemented with mortality cases of coronary heart disease identified in the National Causes of Death Register (1970–2015) that includes all deaths occurring in Denmark. We defined angina pectoris by the International Classification of Diseases Revision 10 code (ICD-10) I20 and the ICD-8 code 413, and myocardial infarction by ICD-10 code I21 and ICD-8 code 410.

Night work

We obtained information on night work from the Danish Working Hour Database, which contains individual day by day information on work hours from 1 January 2007 to 31 December 2015. We defined a night shift as a day with ≥ 3 hours of work between 12:00 AM (midnight) and 5:00 AM.[10] Six time-dependent night work characteristics were constructed at each consecutive day of follow-up: night and day worker, monthly night shifts, cumulative night shifts, years with rotating night shifts, years of any night shift and consecutive night shifts (Box 1). We have previously shown that only 1.1% of men and 1.5% of women of this population were permanent night workers and therefore abstained from including this night work characteristic.[9]

Survey

At the end of follow-up in 2015–16, we e-mailed a questionnaire on smoking, alcohol consumption, height, weight, previous night work and diurnal preference to all currently employed workers ($n = 59\,977$) from three of the five Danish regions.

Statistical analyses

Each health care worker was followed from 1 January 2007 or the first work shift if later, until the day of the first recording of coronary heart disease, death, emigration, disappearance or end of follow-up by 31 December 2015. Associations between night work characteristics (lagged 1 day to secure temporality) and coronary heart disease were analysed with Poisson regression, providing incidence rate ratios (IRR) with 95% confidence intervals (95% CI) with day workers as reference. A priori, we expected no effect modification by sex, but stratified by sex to be able to compare results directly with those of the Vetter *et al.* study that only included women.[1] However, we tested for multiplicative effect modification by interaction terms for sex and the continuous variables of the different night work characteristics among all workers. Analyses were adjusted by age, calendar year, diabetes, obesity, hypercholesterolaemia, hypertension, family history of cardiovascular disease, educational level and

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Box 1. Definition of night work characteristics

Six time-dependent night work characteristics were constructed at each consecutive day of follow-up.

   i) Night and day worker: a health care worker was defined as a night worker from the first night shift, otherwise as a day worker.
  ii) Monthly night shifts: mean number of night shifts per month calculated as the cumulative number of night shifts divided by cumulative months of follow-up (8 categories, rounded up to nearest integer: no night shifts, 1, 2, 3, 4, 5, 6 and >6 night shifts per month).
 iii) Cumulative night shifts: number of night shifts (5 categories: no night shifts, 1–5, 6–30, 31–100 and >100 night shifts, category thresholds defined by quartiles of the cumulative number of night shifts, rounded to the nearest integer divisible by 5).
  iv) Years with rotating night shifts: number of years with ever ≥ 3 night shifts per month and at least 1 day and at least 1 evening shift[1] (4 categories: no night shifts, no rotating night shifts, 1 year and ≥ 2 years, category threshold defined by the median number of years of rotating night shifts). The no rotating night shifts category comprises workers who do not meet the definition, including workers with ≥ 1 night shift and no day or evening shifts for a given year. The latter category may be regarded as permanent nights.
   v) Years of any night shift: number of years with at least 1 night shift (4 categories: no night shifts, <1 year, 1 year and ≥ 2 years, category threshold defined by the median number of years with at least 1 year with any night shift).
  vi) Consecutive night shifts: longest spell of consecutive night shifts (6 categories: no night shifts, never 2 consecutive night shifts, ever 2, ever 3, ever 4 and ever ≥ 5 consecutive night shifts).

In analyses stratified by age or family history of cardiovascular disease, numbers of monthly night shifts were dichotomized by the median among the night workers (0.91 night shifts) because of fewer person-years (and cases) within each stratum.

occupation. Detailed definitions of these variables are available in the Supplementary material (available as Supplementary data at *IJE* online). All covariates were decided upon a priori based on a review of the literature and the availability of relevant information in the registers.[11,12] The different night work characteristics were moderately correlated and we abstained from mutual adjustment to avoid over-adjustment. All *P*-values were two-sided. All night work and covariate variables were treated as time-varying day by day. We tested for linear trends by levels of night work characteristics, with a continuous variable of consecutive integers among all workers and among night workers only.

Based on questionnaire data from end of follow-up, we tabulated the prevalence of self-reported information on smoking, alcohol consumption, body mass index (BMI), night work before 2007 and diurnal preference, by number of monthly night shifts during follow-up.

In supplementary analyses we repeated analyses stratified by age and family history of cardiovascular disease, and we restricted analysis to person-years provided by workers ever working evenings, because evening work has also been associated with increased risk of coronary heart disease and because evening work was unevenly distributed between day and night workers, as shown later.[2–6] In agreement with the EU General Data Protection Regulations (GDPR), we did not report on groups of less than three persons. All analyses were performed with Stata 17 (StataCorp LLC, College Station, TX).

Results

The study population included 100 149 night workers (20 089 men and 80 060 women) and 153 882 day workers (33 650 men and 120 232 women) aged ≥18 years. Mean age (SD) at start of follow-up was 37.7 years (11.0), 36.5 years (11.0), 39.0 years (13.5) and 38.8 years (12.6), respectively. The workers accumulated a total of 1 638 889 person-years at risk and 10 211 077 night shifts. Male and female night workers worked on average 1.8 and 1.7 night shifts per month, respectively. Male night workers had on average 3.2 years of any night shift and 0.8 years of rotating night shifts. For female night workers, these numbers were 3.6 and 0.9. A total of 1090 male workers were diagnosed with coronary heart disease (667 and 0 cases of angina pectoris and 400 and 23 cases of myocardial infarction identified in the national patient and mortality registers, respectively). A total of 2236 women workers were diagnosed with coronary heart disease (1719 and <15 cases of angina pectoris and 503 and <15 cases of myocardial infarction identified in the national patient and mortality registers, respectively).

A total of 672 men died from other causes, 1022 emigrated and 10 disappeared, according to the Danish Civil Registration Register during follow-up. For women these numbers were 1451, 2127 and 8, respectively.

The distributions of age, calendar year, diabetes, obesity, hypercholesterolaemia and hypertension were roughly similar by number of monthly night shifts, except for a higher prevalence of all medical conditions in the category of >6 monthly night shifts (Table 1). The proportion of physicians and those with more education decreased, and the proportion of nurses, auxiliary nurses and those with less education increased, by number of monthly night shifts. Comparable patterns were seen for men and women. Close to 50% of day workers and

nearly all night workers also had evening shifts, except for night workers in the >6 monthly night shifts category.

Male night and day workers showed overall incidence rates of coronary heart disease of 32.3 and 34.2 per 10 000 person-years, respectively. The fully adjusted incidence rate ratio comparing male night with male day workers was 1.22 (95% CI: 1.07, 1.39) (Table 2). Female night and day workers showed overall incidence rate ratios of 16.1 and 17.9 per 10 000 person-years, respectively. The fully adjusted incidence rate ratio was 1.06 (95% CI: 0.97, 1.17).

Among all male workers, there was a 20% increased incidence rate ratio (IRR$_{adj}$ 1.20; 95% CI: 1.02, 1.41) for night workers working 1 night per month compared with day workers. Increased incidence rate ratios were seen for six night shifts per month (IRR$_{adj}$ 2.56; 95% CI: 1.50, 4.37) and for several of the other monthly night work categories. Among male night workers only, six night shifts per month also showed an increased incidence rate ratio (IRR$_{adj}$ 2.19; 95% CI: 1.26, 3.78) but no increase was seen for the other night work categories when compared with the lowest exposure category, and there was no apparent increasing risk with increasing exposure. *P*-values for trend were for all male workers 0.03, and 0.70 for male night workers only.

The incidence rate ratios were 1.71 (95% CI: 1.18, 2.47) and 1.66 (95% CI: 1.14, 2.42) for six night shifts per month among all female workers and female night workers only. No other increases were seen. *P*-values for trend were for all female workers 0.09 and 0.20 for female night workers only. Results for cumulative night shifts, years with rotating night shifts, years with any night shifts, and consecutive night shifts were similar to those seen for monthly night shifts. Few differences were seen between partially adjusted (adjusted for age, calendar year, family history of cardiovascular disease, occupation and educational level, but not diabetes, obesity, hypertension and hypercholesterolaemia) and fully adjusted incidence rate ratios (Supplementary Table S5, available as Supplementary data at *IJE* online; Table 2).

Analyses stratified by age showed increasing risk of coronary heart disease by monthly night shifts for men aged ≥50 years and for women aged 18–39 years, but trend *P*-values were all well above 0.05 when analyses were restricted to night workers only (Supplementary Table S1, available as Supplementary data at *IJE* online).

Among the subset of 34 432 (57% of the eligible) workers who participated in the survey at the end of follow-up, male and female night workers reported lower overall levels of any smoking and alcohol consumption compared with male and female day workers, whereas current BMI levels were comparable (Table 3). However, male and female night workers reported increasing current smoking, current BMI and BMI at age 20, and decreasing alcohol consumption by increasing number of monthly night shifts. Before start of follow-up, 26.9% of male day workers and 50.7% of male night workers reported regular night work which increased with number of monthly night shifts during follow-up. For women day and night workers these numbers were 23.5% and 50.0%, respectively. Night workers, especially women, more often reported being evening persons.

The sensitivity analysis restricted to person-years provided by participants ever working evenings yielded results similar to those obtained from the complete study population (Supplementary Table S2, available as Supplementary data at *IJE* online).

Table 1. Distribution of person-years at risk (%) by number of monthly night shifts among health care workers, Denmark, 2007–15

Worker characteristic	Men (n = 53 739)										Women (n = 200 292)									
	Day worker[b]	Night worker[c]	Monthly night shifts[a]								Day worker[b]	Night worker[c]	Monthly night shifts[a]							
			1	2	3	4	5	6	>6				1	2	3	4	5	6	>6
Person-years	207 846	117 390	61 650	22 170	12 492	6704	3534	1946	8894		791 613	508 360	266 118	90 126	52 990	31 924	18 729	11 617	36 856
Age (years)																			
18–29	20	14	14	15	15	14	15	13	8		18	16	14	20	21	21	19	15	9
30–34	10	17	15	23	21	17	15	15	9		10	17	14	22	22	21	18	16	9
35–39	10	17	15	22	20	16	15	17	13		12	15	15	18	17	17	16	15	12
40–44	10	14	13	13	14	15	15	15	14		12	13	13	12	12	13	14	15	13
45–49	11	12	13	9	10	12	14	13	15		12	12	13	10	10	10	12	13	14
50–54	12	11	12	8	8	11	11	13	15		12	11	12	9	8	8	10	11	14
55–59	11	9	10	6	7	8	8	9	14		11	9	11	7	6	6	7	8	14
60–64	9	6	6	3	4	5	5	5	9		8	5	6	3	3	3	4	5	10
65–69	5	2	3	1	2	2	2	2	3		4	2	2	1	1	1	1	2	4
≥70	1	0	0	0	0	0	0	0	0		1	0	0	0	0	0	0	0	1
Calendar year of follow-up																			
2007[d]	6	4	2	4	6	9	10	9	8		7	5	3	5	6	8	9	10	10
2008	9	7	6	7	10	12	12	10	10		9	8	7	8	9	11	12	11	11
2009	10	9	8	9	11	11	11	10	11		10	10	9	10	11	11	11	11	11
2010	10	11	10	11	12	11	11	10	11		11	11	11	11	11	12	11	11	11
2011	11	12	12	12	12	11	11	11	11		11	12	12	12	12	11	11	11	11
2012	12	13	13	13	12	11	11	12	12		12	13	13	13	12	11	11	11	11
2013	13	14	14	14	12	11	11	12	12		13	13	14	14	13	12	11	11	11
2014	14	15	16	15	13	11	12	13	13		14	14	15	14	13	12	12	12	11
2015	15	16	18	16	13	12	12	13	13		14	15	16	15	13	12	12	11	11
Diabetes[e]	3.4	3.1	3.1	2.6	3.0	2.5	3.6	2.8	4.6		3.1	3.1	3.0	3.1	3.0	2.7	2.6	3.2	4.3
Obesity[e]	4.7	5.8	5.8	4.8	5.7	5.6	6.1	6.9	8.2		16.7	18.2	18.1	16.5	16.4	17.6	18.3	20.6	26.2
Hypercholesterolaemia and hyperlipidaemia[e]	9.4	7.0	7.3	5.8	5.8	5.8	7.8	7.5	10.0		6.9	5.1	5.7	3.5	3.5	3.4	3.8	4.1	8.8
Essential hypertension[f]	20.2	18.2	19.0	16.5	17.2	15.5	15.9	14.6	22.0		26.4	23.5	24.9	20.9	19.4	20.3	20.0	21.5	30.5
Family history of cardiovascular disease[f]	12.1	13.8	14.2	12.1	13.6	13.4	15.1	15.4	15.6		12.4	13.4	13.3	13.4	13.5	12.8	13.6	14.8	13.9
Educational level																			
≤10 years	14	10	9	7	9	11	15	16	19		11	2	2	1	1	2	2	2	7
11–13 years	33	26	26	18	20	25	31	38	52		37	23	22	17	17	20	22	28	46
>13 years	53	64	65	75	71	64	55	46	29		52	75	76	82	82	79	77	71	47
Occupation																			
Physicians[g]	17	37	34	56	52	41	23	11	2		3	10	10	17	13	8	4	2	0
Nurses and midwives[h]	2	10	8	10	11	14	20	23	13		18	55	51	58	64	67	69	64	40
Auxiliary nurses, janitors and orderlies[i]	35	35	33	27	30	34	41	53	74		29	24	24	18	18	20	23	30	54
Other higher skilled occupations[j]	36	14	20	8	6	8	12	10	10		46	11	16	8	5	5	5	4	6
Other less skilled occupations[k]	10	3	5	0	1	2	5	2	2		4	0	0	0	0	0	0	0	0
Ever evening work[L]	46	96	99	99	99	98	97	96	68		52	96	99	99	98	96	95	92	68

ISCO-08, International Standard Classification of Occupations 2008.

[a] Mean number of night shifts per month at end of study, rounded up to nearest integer.
[b] No night shifts since entry.
[c] Ever ≥1 night shift since entry.
[d] Data available for four of five regions.
[e] A hospital diagnosis or a prescribed medication.
[f] A hospital diagnosis.
[g] ISCO-08 codes 2210, 2211 and 2212.
[h] ISCO-08 codes 2221 and 2222.
[i] ISCO-08 codes 3221, 9112, 9121 and all 5000-series ISCO-08 codes except 5000, 5120, 5153, 5411 and 5419.
[j] Other ISCO-08 codes in series 1000, 2000, 3000 and 4000.
[k] Other ISCO-08 codes in series 5000, 6000, 7000, 8000 and 9000.
[L] Ever ≥1 evening shift since entry.

Table 2. Night work characteristics and risk of coronary heart disease among health care workers, Denmark, 2007–15

Night work characteristic	Men (n = 53 739) Cases	Person-years	IR[a]	Day and night workers IRR[b] (95% CI)	Night workers only IRR[b] (95% CI)	Women (n = 200 292) Cases	Person-years	IR[a]	Day and night workers IRR[b] (95% CI)	Night workers only IRR[b] (95% CI)
Day worker[c]	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
Night worker[d]	379	117 390	32.3	1.22 (1.07–1.39)		819	508 360	16.1	1.06 (0.97–1.17)	
Monthly night shifts[e]										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
1 night shift/month	206	61 650	33.4	1.20 (1.02–1.41)	1.00	456	266 118	17.1	1.04 (0.93–1.16)	1.00
2 night shifts/month	51	22 170	23.0	1.16 (0.87–1.55)	0.99 (0.72–1.35)	109	90 126	12.1	1.06 (0.87–1.29)	1.02 (0.82–1.26)
3 night shifts/month	39	12 492	31.2	1.45 (1.04–2.01)	1.22 (0.86–1.72)	52	52 990	9.8	0.88 (0.66–1.16)	0.84 (0.63–1.12)
4 night shifts/month	19	6704	28.3	1.17 (0.74–1.86)	0.99 (0.61–1.58)	52	31 924	16.3	1.38 (1.04–1.82)	1.32 (0.99–1.77)
5 night shifts/month	9	3534	25.5	0.93 (0.48–1.81)	0.79 (0.40–1.54)	19	18 729	10.1	0.77 (0.49–1.22)	0.74 (0.47–1.18)
6 night shifts/month	14	1946	71.9	2.56 (1.50–4.37)	2.19 (1.26–3.78)	29	11 617	25.0	1.71 (1.18–2.47)	1.66 (1.14–2.42)
>6 night shifts/month	41	8894	46.1	1.10 (0.80–1.52)	0.95 (0.67–1.36)	102	36 856	27.7	1.12 (0.91–1.37)	1.09 (0.87–1.36)
P for trend				0.03	0.70				0.09	0.20
Cumulative night shifts										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
1–5 night shifts	112	31 939	35.1	1.20 (0.98–1.47)	1.00	239	124 849	19.1	1.09 (0.95–1.25)	1.00
6–30 night shifts	92	32 295	28.5	1.20 (0.96–1.50)	1.02 (0.77–1.35)	208	149 066	14.0	0.99 (0.85–1.15)	0.91 (0.75–1.10)
31–100 night shifts	83	30 359	27.3	1.26 (1.00–1.60)	1.10 (0.82–1.47)	179	130 485	13.7	1.08 (0.92–1.27)	0.99 (0.81–1.20)
>100 night shifts	92	22 797	40.4	1.22 (0.97–1.53)	1.07 (0.81–1.43)	193	103 960	18.6	1.10 (0.94–1.28)	1.02 (0.84–1.24)
P for trend				<0.01	0.54				0.23	0.71
Years with rotating night shifts[f]										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
No rotating night shifts	248	76 222	32.5	1.23 (1.06–1.42)		536	325 505	16.5	1.05 (0.95–1.17)	
1 year with rotating night shifts	69	25 537	27.0	1.10 (0.86–1.42)	1.00	152	106 677	14.2	1.02 (0.86–1.21)	1.00
≥2 years with rotating night shifts	62	15 631	39.7	1.33 (1.02–1.74)	1.18 (0.83–1.68)	131	76 179	17.2	1.17 (0.97–1.41)	1.12 (0.88–1.43)
P for trend				<0.01	0.36				0.14	0.35
Years with any night shifts[g]										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
<1 year with night shifts	37	14 160	26.1	1.42 (1.01–2.01)	1.00	75	58 337	12.9	1.25 (0.97–1.61)	1.00
1 year with night shifts	126	40 181	31.4	1.19 (0.98–1.44)	0.85 (0.55–1.31)	263	160 811	16.4	1.08 (0.94–1.23)	0.77 (0.56–1.07)
≥2 years with night shifts	216	63 048	34.3	1.20 (1.02–1.42)	0.87 (0.56–1.34)	481	289 213	16.6	1.02 (0.91–1.15)	0.73 (0.52–1.01)
P for trend				<0.01	0.80				0.46	0.12
Consecutive night shifts										
No night shifts	711	207 846	34.2	1.00		1417	791 613	17.9	1.00	
Never 2 consecutive night shifts	156	53 957	28.9	1.21 (1.01–1.45)	1.00	248	151 957	16.3	1.02 (0.89–1.18)	1.00
Ever 2 consecutive night shifts	56	18 905	29.6	1.33 (1.01–1.76)	1.13 (0.83–1.53)	139	78 917	17.6	1.10 (0.92–1.31)	1.07 (0.86–1.32)
Ever 3 consecutive night shifts	38	11 617	32.7	1.13 (0.81–1.58)	0.97 (0.67–1.40)	155	112 359	13.8	0.99 (0.84–1.18)	0.96 (0.78–1.18)
Ever 4 consecutive night shifts	35	9697	36.1	1.32 (0.93–1.86)	1.12 (0.76–1.65)	114	86 624	13.2	1.12 (0.92–1.37)	1.09 (0.86–1.37)
Ever ≥5 consecutive night shifts	94	23 213	40.5	1.18 (0.94–1.47)	1.00 (0.75–1.33)	163	78 503	20.8	1.12 (0.95–1.33)	1.10 (0.89–1.36)
P for trend				0.03	0.97				0.13	0.39

[a] Incidence rate per 10 000 person-years.
[b] Incidence rate ratio, adjusted for age, diabetes, obesity, hypercholesterolaemia, hypertension, family history of cardiovascular disease, calendar year, occupation and educational level.
[c] No night shift since entry.
[d] Ever ≥1 night shift since entry.
[e] Mean number of night shifts per month, rounded up to nearest integer.
[f] Years with ever >3 night shifts per month and ≥1 day shift and ≥1 evening shift. The 'no rotating night shifts' category was not included in the trend analyses.
[g] Years with ≥1 night shifts.

Table 3. Smoking, alcohol consumption, BMI, regular night work before 2007 and diurnal preference among a subset of health care workers, Denmark, 2015–16

Worker characteristic	Day worker[a]	Night worker[b]	P	Monthly night shifts[c]							P for trend
				1	2	3	4	5	6	>6	
Men (n = 5753)	2889	2864		1694	623	256	79	64	28	120	
Smoking[d] (%)											
Any smoking	48.4	45.5	0.02	46.8	34.5	41.4	62.0	67.2	67.9	65.0	0.07
Current smoking	11.6	12.9	0.15	12.3	10.0	12.5	13.9	32.8	14.3	25.0	<0.001
Previous smoking	36.8	32.7	0.001	34.5	24.6	28.9	48.1	34.4	53.6	40.0	0.27
Alcohol consumption (average units per week)[e,f]	6.1	5.7	0.04	6.0	6.1	4.9	5.3	3.8	1.9	4.1	<0.001
BMI, current (mean kg/m^2)[f]	25.9	25.9	0.66	26.0	25.3	25.9	26.4	27.0	28.2	27.5	<0.001
BMI, at age 20 years (mean kg/m^2)[f]	23.1	23.3	0.05	23.3	23.1	22.9	23.4	23.9	23.9	23.8	0.01
Regular night shift work before 2007 (%)[g]	26.9	50.7	<0.001	46.9	52.3	59.4	63.3	51.6	64.3	65.8	<0.001
Diurnal preference (%)											
Definitely morning person	22.0	19.0	0.003	19.9	16.5	20.3	25.3	17.2	10.7	14.2	0.001
Mostly morning person	30.8	27.8	0.008	28.5	28.9	28.1	25.3	20.3	21.4	17.5	<0.001
Mostly evening person	34.3	36.9	0.049	36.7	40.5	34.4	36.7	37.5	32.1	29.2	0.79
Definitely evening person	11.8	15.8	<0.001	14.3	13.6	16.4	12.7	25.0	35.7	38.3	<0.001
Women (n = 28 679)	14 240	14 439		8458	2517	1347	778	487	272	580	
Smoking[d] (%)											
Any smoking	43.8	40.9	<0.001	42.0	37.8	37.3	40.0	38.6	42.7	50.5	0.02
Current smoking	10.1	9.8	0.38	9.3	8.8	9.6	9.9	12.1	10.7	20.9	<0.001
Previous smoking	33.6	31.1	<0.001	32.7	29.0	27.7	30.1	26.5	32.0	29.7	<0.001
Alcohol consumption (average units per week)[e,f]	2.8	2.5	<0.001	2.6	2.4	2.2	2.2	2.2	2.3	1.9	<0.001
BMI, current (mean kg/m^2)[f]	24.9	24.8	0.16	24.6	24.8	24.8	25.2	25.4	25.6	26.9	<0.001
BMI, at age 20 years (mean kg/m^2)[f]	21.8	22.1	<0.001	21.9	22.3	22.2	22.5	22.5	22.5	23.0	<0.001
Regular night shift work before 2007 (%)[g]	23.5	50.0	<0.001	48.0	47.5	51.6	51.9	60.8	64.0	68.3	<0.001
Diurnal preference (%)											
Definitely morning person	25.6	19.0	<0.001	20.8	18.0	16.0	16.5	15.2	15.1	12.2	<0.001
Mostly morning person	36.1	32.9	<0.001	33.7	33.5	33.6	35.6	30.4	26.8	19.0	<0.001
Mostly evening person	29.7	35.6	<0.001	34.7	36.7	37.8	33.3	38.0	41.5	36.6	<0.001
Definitely evening person	8.0	11.9	<0.001	10.1	11.2	12.3	13.9	16.0	16.5	31.9	<0.001

BMI, body mass index.
a No night shifts since entry.
b Ever ≥1 night shift since entry.
c Mean number of night shifts per month at end of study, rounded up to nearest integer.
d <1% missing.
e 1 unit of alcohol is equal to 12 g of alcohol.
f 2% missing.
g 5% of responses are incomplete and cannot be categorized.

Stratified analyses showed increasing risk of coronary heart disease by monthly night shifts for men with no family history of cardiovascular disease, but trend *P*-values were all above 0.05 when restricted to night workers only (Supplementary Table S3, available as Supplementary data at *IJE* online).

The interaction terms between sex and the night work characteristics showed *P*-values in the range 0.09–0.70. Analyses combining the two sexes showed overall increased risk of coronary heart disease for night workers compared with day workers (IRR 1.11; 95% CI: 1.03, 1.20). Among the night workers only, no obvious trends were seen by any of the night work characteristics (Supplementary Table S4, available as Supplementary data at *IJE* online).

Discussion

This study showed an overall increased incidence rate ratio of coronary heart disease of about 20% for male night workers compared with male day workers. Highest risks were observed in top exposure categories for several night work characteristics. Incidence rate ratios increased steeply to the 20% level without further consistent increase with increasing number of monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shifts or consecutive night shifts. No overall increased risk of coronary heart disease was apparent for women.

Comparisons with other studies

This study was inspired by Vetter *et al.*'s report of the Nurses' Health Study showing increasing risk of coronary heart disease in women by increasing years with rotating night shifts, but we did not corroborate their findings.[1] Brown *et al.* and Gu *et al.* also reported increasing risk of coronary heart disease by increasing years with rotating night shifts among women in the Nurses' Health Study population.[13,14] Our study's finding of an overall increased risk of coronary heart disease among male night workers is in line with a long series of earlier studies.[3–5] However, Yadegarfar *et al.* and Yong *et al.*, observed no associations with years of night work in two independent male worker populations.[15,16]

Wang *et al.* observed increasing risk of coronary heart disease with increasing lifetime duration of night shifts for both sexes combined.[17] Torquati *et al.* did not find that sex explained heterogeneity in the relation between shift work and cardiovascular disease across 21 studies included in a meta-regression analysis.[5] Others have found that women are less tolerant to shift work than men, eg, related to more sleep problems and higher levels of fatigue and sleepiness.[18] Taken together, these studies do not provide consistent support for a

sex-specific effect of night work and we observed no statistical interaction by sex.

However, in this study, a night worker was defined by one or more night shifts during follow-up, which is a much wider criterion than in other studies and a cautious comparison of results is warranted. The male and female night workers worked on average 1.8 and 1.7 night shifts per month, respectively, for an average of less than 4 years, and one may thus speculate if this intensity and duration of night work for most workers was below a threshold. In the Vetter *et al.* study, increased risks were seen following 5 or more years of at least three night shifts per month.[1]

The steep increase in incidence rate ratios (eg, from zero to one monthly night shift or from zero to one ranging to five cumulative night shifts) seen among men can hardly be explained by night work per se but points towards other risk factors for coronary heart disease unevenly distributed between male night and day workers. The no increased overall risk of coronary heart disease in women night workers is in contrast with most earlier studies.[3–5]

Limitations and strengths of the study

The lack of information on distant night work, before start of follow-up, is a limitation. The survey data, however, showed increasing prevalence of regular night work before start of follow-up, with increasing number of monthly night shifts during follow-up. On the premise that distant night work is causally related with coronary heart disease, such exposure misclassification could have inflated the response relation with the more recent night work of this study, and cannot explain the null findings.

The high prevalence of night work in the study population before start of follow-up documents that this was not an inception population of newly hired workers. This may have resulted in the inclusion of more night workers less susceptible to night work, which may have deflated real associations and this could at least partly explain the lack of exposure-response patterns.[19] Our population did not allow the definition of an inception population of newly hired workers with a sufficient number of male ($n = 95$) and female ($n = 210$) cases of coronary heart disease for meaningful analysis. However the strongest study so far, the Vetter *et al.* study, showed increased risk of coronary heart disease particularly following recent night work expected to be less influenced by such a selection process.

The population includes few permanent night workers which allowed for no meaningful analyses of risk of coronary heart disease.

A major strength of the study is the detailed day by day information on night work, allowing analyses of quantitative night work characteristics. Since salary depends on working hours, recordings are expected to be complete, precise and valid, given that employers and employees have a common interest in their correctness.[20] Recordings were obtained before diagnoses of coronary heart disease were made and they were therefore unaffected by recall; this may have biased studies relying on self-reports.[3,6] Thus we find that recall bias cannot either explain the negative exposure-response results.

From the payroll registers we had access to, all health care workers of all public hospitals regardless of occupation, workhours and duration of employment since 2007. For this population we had access to all inpatient and outpatient hospital contacts since 1994 as recorded in a national register with high coverage. In Denmark, access to the health care system including hospitals is tax funded, and we thus find that selection bias is an unlikely explanation of our finding of no exposure-response relation.

Cases of coronary heart disease were identified in a national register with 88–93% positive predictive values for first-time diagnoses of angina pectoris and 97% for myocardial infarction, when compared with medical records.[21] Thus, non-differential misclassification of coronary heart disease should not have biased our findings substantially towards the null. The almost complete follow-up of cohort members makes notable social-based selection bias unlikely.

Adjustment was done for known medical risk factors, family history, occupation, educational level, age and calendar year, based on data from national registers with high coverage. Restricting analyses to person-years provided by participants ever working evenings did not affect results. Age was a confounder and was adjusted for in all analyses, and a supplementary analysis stratifying by age did not change findings. Night work has been suggested to increase the risk of type 2 diabetes, obesity, hypertension and hypercholesterolaemia which may be on the path between night work and coronary heart disease.[22–25] Adjusting for these factors may thus have blurred real associations, but including them in the models did not change the partially-adjusted estimates much, and it is unlikely that the fully adjusted analyses are over-adjusted by mediating health factors.

The survey information on smoking, alcohol consumption, BMI and diurnal preference, which was available for a non-random subgroup at the end of follow-up in 2015–16, showed increasing level of smoking and BMI by increasing number of monthly night shifts among the night workers. To the extent that these results are representative of the total study population during follow-up 2007–15, they indicate that our exposure-response analyses have been confounded and overestimate the true values even if the survey data showed decreasing alcohol consumption by increasing number of monthly night shifts. The survey data were, however, obtained from a survivor population and may not be representative and included only 14% of all workers, and for that reason we abstained from including them in adjusted analyses. The survey showed lower overall levels of smoking and alcohol consumption and comparable BMI levels among the male night workers compared with the male day workers, and provided thus no obvious clues to the causes of the increased risk of coronary heart disease seen in male night workers. Day workers never working nights may be fundamentally different from night workers with respect to risk factors that we were unable to document or account for in the analyses and, as such, may not be a suitable reference category. A similar phenomenon was seen for breast cancer in a female subpopulation of the current study[26] and in other occupational cohorts.[27,28] For that reason, the internal trend analyses conducted within night workers only, who are expected to be more homogeneous with respect to unrecognized confounders, are regarded as the most valid.

Conclusion

This study provides evidence for a 20% increased risk of coronary heart disease among men with night shifts, as recorded day by day since 2007. Highest risks were observed in top exposure categories for several night work characteristics. However, no evidence was provided for linear exposure-response relations or other clear association patterns between monthly night shifts, cumulative night shifts, years with rotating night shifts, years of any night shift or consecutive shifts

and coronary heart disease risk among men and women. This indicates that reducing the extent of these night work characteristics would not reduce the risk of coronary heart disease in low-exposed populations such as the current cohort. Results from this low-exposed population may not be applicable for higher-exposed populations.

Ethics approval

Data availability

No additional data available. For legal and ethical reasons, individual-level data cannot be shared by the authors and are only accessible to authorized researchers after application to the Danish Health Data Authority.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

J.M.V. and H.A.K. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: J.M.V. and H.A.K. Acquisition, analysis or interpretation of data: J.M.V., H.A.K. and A.D. All authors contributed to interpretation of data. Drafting the manuscript: J.M.V. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: J.M.V. in close collaboration with H.A.K. Administrative, technical or material support: J.M.V., H.A.K. and A.D. Supervision: H.A.K. and A.D.

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Conflict of interest

None declared.

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