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Evidence on the association between shift work and mortality is limited. We found significantly enhanced all-cause, cardiovascular and diabetes mortality among nurses with night and evening shifts. We present novel finding of an increase in mortality from Alzheimer's disease and dementia, and potentially psychological disorders among night, evening, and rotating shift workers.

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Key terms: all-cause mortality; Alzheimer's disease; cancer; cardiovascular disease; cause-specific mortality; cohort study; Danish nurse cohort; dementia; diabetes; night shift work; nurse; nursing; psychiatric disease; shift work; shift worker

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Shift work and overall and cause-specific mortality in the Danish nurse cohort

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Objectives Evidence of an effect of shift work on all-cause and cause-specific mortality is inconsistent. This study aims to examine whether shift work is associated with increased all-cause and cause-specific mortality.

Methods We linked 28 731 female nurses (age ≥44 years), recruited in 1993 or 1999 from the Danish nurse cohort where they reported information on shift work (night, evening, rotating, or day), to the Danish Register of Causes of Death to identify deaths up to 2013. We used Cox regression models with age as the underlying scale to examine the associations between night, evening, and rotating shift work (compared to day shift work) and all-cause and cause-specific mortality in models adjusted for potentially confounding variables.

Results Of 18 015 nurses included in this study, 1616 died during the study time period from the following causes: cardiovascular disease (N=217), cancer (N=945), diabetes (N=20), Alzheimer's disease or dementia (N=33), and psychiatric diseases (N=67). We found that working night [hazard ratio (HR) 1.26, 95% confidence interval 95% CI) 1.05–1.51] or evening (HR 1.29, 95% CI 1.11–1.49) shifts was associated with a significant increase in all-cause mortality when compared to working day shift. We found a significant association of night shift work with cardiovascular disease (HR 1.71, 95% CI 1.09–2.69) and diabetes (HR 12.0, 95% CI 3.17–45.2, based on 8 cases) and none with overall cancer mortality (HR 1.05, 95% CI 0.81–1.35) or mortality from psychiatric diseases (HR 1.17, 95% CI 0.47–2.92). Finally, we found strong association between evening (HR 4.28, 95% CI 1.62–11.3) and rotating (HR 5.39, 95% CI 2.35–12.3) shift work and mortality from Alzheimer's disease and dementia (based on 8 and 14 deaths among evening and rotating shift workers, respectively).

Conclusions Women working night and evening shifts have increased all-cause, cardiovascular, diabetes, and Alzheimer's and dementia mortality.

Key terms all-cause mortality; Alzheimer's disease; cancer; cardiovascular disease; cohort study; dementia; diabetes; night shift work; nursing; psychiatric disease; shift worker.

It has been suggested that working outside normal work hours, especially at night, has negative health effects (1, 2), but evidence of an effect of shift work on all-cause mortality is inconsistent (3–12). Several studies (4–6,10), including a recent meta-analysis (13), have reported an increase in all-cause mortality among shift workers, but only a few have detected a statistically significant association (4, 6, 13) while others have found none (3, 9, 12, 14) or inverse an association (7).

In 2007, an International Agency for Research on Cancer (IARC) working group classified shift work involving circadian disruption as "probably carcinogenic" to humans (group 2A) (15). The majority of recent studies on the health effects of night shift work have focused on female breast cancer incidence (16), and only a few have examined cancer mortality (5–7). One study found significantly increased mortality from any cancer among female but not among male shift workers (5). Few studies have examined shift work and cancer-specific mortality (6, 7, 17–19). Gu et al (6) found an association with lung cancer mortality and working shifts ≥15 years among American female nurses after adjustment for potential confounders including tobacco smoking. Yong et al (7), found no

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increase in lung cancer mortality among male chemical shift workers. Carter et al (19) detected an association between rotating shift work and ovarian cancer mortality, whereas Lin et al (17, 18) found no association between shift work and either pancreatic or biliary tract cancer mortality.

Shift work has been linked to an increased incidence of coronary or ischemic heart disease (IHD) (20, 21) and diabetes (2, 22), but there is limited evidence on mortality due to cardiovascular disease (CVD) (23) and diabetes (12). To date, no studies have examined the effect of shift work on Alzheimer's disease, dementia or psychiatric diseases, despite the fact that poor sleep and sleep deprivation have been linked to increased risk of cognitive and neurodegenerative outcomes (24–26). In this study, we examine the association between shift work and all-cause mortality and mortality due to CVD, cancer, diabetes, neurodegenerative and psychiatric diseases in the Danish nurse cohort (DNC).

Methods

Study population

The DNC study (27) was initiated in 1993, when 23 170 female members of the Danish Nurses Organization aged >44 years were invited to participate in this nationwide study inspired by the American Nurses' Health Study. A total of 19 898 (86%) responded positively. In 1999, the cohort was expanded, adding an additional 10 534 nurses aged 44 years, 8833 (84%) of whom agreed to participate. Cohort participation involved answering a comprehensive self-administrated questionnaire on lifestyle, health, use of hormones and occupational characteristics, including working hours and the work environment. Using a unique personal identification number, we linked the DNC to the Danish Civil Registration System (28) in order to obtain information on cohort participants' vital status (death, emigration, disappearance, etc) during follow-up until 2013.

Shift work definition

Shift work data was self-reported by nurses who were in the workforce at the time of recruitment (excluding those who were retired, on sick leave, or unemployed) and nurses who answered the following question on shift work status: "Do you normally work in: a) day, b) evening, c) night, or d) rotating shifts?". Rotating shifts can be working either day (typically 07:00–15:00 hours) and evening (15:00–23:99 hours) or day, evening and night (23:00–07:00 hours).

Health outcomes

Information on the deceased cohort participants' causes of death was obtained from the Danish Register of Causes of Death (29), which contains information on all deaths of Danish residents dying in Denmark. Causes of deaths are coded according to the World Health Organization's International Classification of Diseases (ICD) version-10 (after 1994) or ICD-8 (before 1994). All death certificates have underlying cause of death and up to four contributory causes of death, which are not mandatory. We examined all-cause mortality as all deaths occurring during follow-up, including 38 deaths registered in the Civil Registration System with missing cause of death data (no record in the Register of Causes of Deaths). We examined the following cause-specific causes of death using the underlying cause of death: total CVD (ICD-10: I00-99, ICD-8: 4010, 4100, 4129, 4279, 4339, 4369, 4412, 4500), IHD (ICD-10: I20-25, ICD-8: 4100, 4129), stroke (ICD-10: I60-69, ICD-8: 4339, 4369), other CVD (ICD-10: I00-09, I26-28, I30-50, I70-99, ICD-8: 4279, 4412, 4500), all-cancer (ICD-10: C00-97 & ICD-8: 1578-79, 1538, 1740, 1621, 1830, 2022, 2041), breast cancer (ICD-10: C50, ICD-8: 1740), lung cancer (ICD-10: C33-34, ICD-8: 1621), ovarian cancer ICD-10: C56, C570-574, ICD-8: 1830), pancreatic cancer (ICD-10: C25, ICD-8: 1578-1579), and colorectal cancer (ICD-10: C18-19, C20, C21, ICD-8: 1538). Additionally, we defined the following cause-specific mortality outcomes based on underlying or contributing cause of death: hypertension (ICD-10: I10-15, ICD-8: 4010); diabetes (ICD-10: E10-14), Alzheimer's and dementia, combined (ICD10: F00-01, F03, G30), psychiatric and behavioral diseases, combined (ICD-10: F01, F03-99, ICD-8: 2990, 3032, 3040, 5710, 9779).

Statistical analysis

Cox proportional hazard regression model with age as the underlying time scale, was used to analyze mortality (all-cause and cause-specific) as a function of shiftwork, in two different models: crude (age-adjusted as age is underlying time scale) and fully adjusted, additionally adjusted for (i) smoking (never/past/current); (ii) pack-years [defined as 20 cigarettes/day per year, calculated from smoking intensity (number of cigarettes a day) and smoking duration (years)]; (iii) leisure-time physical activity [categorized in low/medium/high and based on the following question: "Which of the following statements describes you best? (a) Exercise heavily and do competitive sports regularly or several times a week; (b) Do sports/heavy gardening or similar ≥4 hours a week; (c) walk, bike or doing other light exercise ≥4 hours a week; (d) Reading, watching television or other sedentary activities"]; (iv) body mass index (BMI) [cal-

Table 1. Characteristics of 18 015 nurses at baseline (1993 and 1999) by status (active/dead) at end of follow-up (31 December 2012).

	Total		Alive		Dead [a]		P-value [b]
	N	%	N	%	N	%	
Total	18 015	100	16 399	91.0	1616	9.0	
Person-years	316 644	100	296 468	93.6	20 176	6.4	
Work type							
Day	11 272	62.6	10 338	63.0	934	57.8	<0.001
Evening	1805	10.0	1569	9.6	236	14.6	
Night	980	5.4	829	5.1	151	9.3	
Rotating	3958	22.0	3663	22.3	295	18.3	
Body mass index (kg/m^2)							
<18.5	354	2.0	291	1.8	63	3.9	<0.001
18.5–24.9	12 688	70.4	11 593	70.7	1095	67.8	
25–29.9	3864	22.0	3613	22.0	351	21.7	
≥30	1009	5.6	902	5.5	107	6.6	
Smoking status							
Never	6725	37.3	6323	38.6	402	24.9	<0.001
Past	5244	29.1	4877	29.7	367	22.7	
Current	6046	33.6	5199	31.7	847	52.4	
Number of pack years [c]							
≤10	5096	28.3	4745	28.9	351	21.7	<0.001
11–20	2942	16.3	2695	16.4	247	15.3	
>20	3252	18.1	2636	16.1	616	38.1	
Never-smokers	6725	37.3	6323	38.6	402	24.9	
Alcohol consumption (drinks/week)							
0	2190	12.2	1929	11.8	261	16.2	<0.001
1–14 (moderate)	11 522	64.0	10 607	64.7	915	56.6	
>15 (heavy)	4303	23.9	3863	23.6	440	27.2	
Physical activity							
Low	956	5.3	817	5.0	139	8.6	<0.001
Medium	11 906	66.1	10 803	65.9	1103	68.3	
High	5153	28.6	4779	29.1	374	23.1	
Diet							
Consume vegetables on daily basis	17 787	98.7	16 214	98.9	1573	97.3	<0.001
Consume fruit on daily basis	17 387	96.5	15 856	96.	1531	94.7	<0.001
Avoids fatty meat	16 470	91.4	15 060	91.8	1410	87.3	<0.001
Self-reported preexisting diseases							
Hypertension	1890	10.5	1619	9.9	271	16.8	<0.001
Diabetes	158	0.9	134	0.8	24	1.5	0.006
Myocardial infarction	47	0.3	32	0.2	15	0.9	<0.001
Self-reported health							
Very good	7994	44.4	7463	45.5	531	32.9	<0.001
Good	7940	44.1	7170	43.7	770	47.6	
Moderate	1894	10.5	1624	9.9	270	16.7	
Bad	166	0.9	129	0.8	37	2.3	
Very bad	21	0.1	13	0.1	8	0.5	
Working status							
Working	17 924	99.5	16 313	99.5	1611	99.7	0.43
Homeworker	1	<0.1	1	<0.1	0	0.0	
Retired	9	<0.1	8	<0.1	1	0.1	
Unemployed/rehabilitation	4	<0.1	3	<0.1	1	0.1	
Other	77	0.4	74	0.5	3	0.2	
Stressful work environment							
Never	251	1.4	205	1.3	46	2.8	<0.001
Rarely	2847	15.8	2579	15.7	268	16.6	
Occasionally	7788	43.2	7072	43.1	716	44.3	
Often	5713	31.7	5245	32.0	468	29.0	
Almost always	1416	7.9	1298	7.9	118	7.3	
Marital status							
Married	13 476	74.8	12 404	75.6	1072	66.3	<0.001
Separated	328	1.8	292	1.8	36	2.2	
Divorced	2094	11.6	1876	11.4	218	13.5	
Single	1405	7.8	1230	7.5	175	10.8	
Widow	712	4.0	597	3.6	115	7.1	
Use of hormone therapy							
Never-users	13 664	75.8	12 607	76.9	1057	65.4	<0.001
Ever-users	4351	24.2	3792	23.1	559	34.6	
Use of oral contraceptives							
Never-users	5788	32.1	5045	30.8	743	46.0	<0.001
Ever-users	12 227	67.9	11 354	69.2	873	54.0	
Births							
0	1978	11.0	1720	10.5	258	16.0	<0.001
≥1	16 037	89.0	14 679	89,5	1358	84.0	

[a] All-cause mortality.

[b] Nurse who were alive and dead at end of follow-up were compared using Pearson's Chi-squared for categorical variables.

[c] One pack year was defined as 20 cigarettes/year in ever-smokers.

culated from self-reported height and weight (kg/m^2)]; (v) alcohol consumption (number of drinks per week/ none, moderate 1–14, heavy ≥15); (vi) diet ["How often do you eat vegetables and fruits?" (a) Rarely or never, (b) a couple of times a week, (c) daily, or (d) several times a day" and "Do you avoid fatty meat? (yes/no)"]; (vii) pre-existing diseases [based on whether or not participants reported being diagnosed or taking medication to treat the disease hypertension, diabetes or myocardial infarction (MI)]; self-reported health ["How would you evaluate your present state of health? (a) very good, (b) good, (c) moderate, (d) bad, or (e) very bad"]; (viii) work stress ["How often are you so busy that you have difficulties in doing your work tasks? (a) never, (b) rarely, (c) occasionally, (d) often, (e) almost always"]; (ix) marital status (married/separated/divorced/single/ widow); (x) female reproductive factors (a) births ["How many children have you given birth to?", dichotomized into 0/≥1], (b) use of hormone therapy ["Are you or have you previously been on hormone replacement therapy (HRT) with estrogen? (No, I have never been in hormone replacement therapy/I have previously been in hormone replacement therapy/ I am currently in hormone replacement therapy)"], and (c) oral contraceptives ["Have you ever used oral contraceptives? (yes/ no)"]. Analysis of breast and ovarian cancer mortality were additionally adjusted for number of births and age at first birth. Lastly, we examined whether BMI or a stressful work environment acted as a mediating factors in the association between shift work and all-cause mortality, by examining changes in risk estimates with and without adjustment for BMI and work stress in the fully adjusted model.

Results

Of the 28 731 participants in the DNC, 10 716 were excluded for the following reasons: (i) emigration prior to cohort baseline (N=4), (ii) retired, unemployed or on sick leave at the time of cohort recruitment (N=6721), (iii) missing information on shift work schedule (N=669), and (iv) missing information on ≥1 potentially confounding variable(s) (N=3322). The final analysis comprised 18 015 participants. Mean follow-up was 17.6 years, giving a total 316 644 person-years, during which 1616 nurses died, including 217 from CVD, 945 from cancer, 20 from diabetes, 33 from Alzheimer's or dementia, and 67 from psychiatric diseases.

A majority of the nurses worked day shifts (62.6%), followed by rotating (22.0%), evening (10.0%) and permanent night (5.4%) shifts at the time of recruitment (table 1). Night and evening shift work were more prevalent among nurses who died (9.3% and 14.6%) than among those who were alive (5.1% and 9.6%) at the end of follow-up. Nurses who died were older at the recruitment (mean age 54.2 years) than nurses who were alive at the end of follow-up (mean age 49.9 years). Furthermore, nurses who died smoked more, used HRT more frequently, and less oral contraceptives than nurses who remained alive at the end of follow-up.

Nurses working night shifts were more likely to be current smokers, overweight and obese, and HRT users, but less likely to be married than nurses working other shifts (table 2). Nurses working rotating shifts were more similar to those working day shift than those working night shifts. Mean age [standard deviation (SD)] at baseline was 50.2 (4.7), 51.6 (5.5), 52.9 (5.6) and 49.2 (4.3) years for day, evening, night and rotating shift workers, respectively.

Compared to nurses working day shifts, we found a statistically significant increase in all-cause mortality among nurses working evening [hazard ratio (HR): 1.53, 95% confidence interval (95% CI) 1.33–1.77] and night (HR 1.74, 95% CI 1.48–2.07) shifts, and no increase in those working rotating shifts in the crude model. Estimates were attenuated, but remained statistically significant in the fully adjusted model for evening (HR1.29, 95% CI 1.11–1.49) and night (HR 1.26, 95% CI 1.05–1.51) shifts (table 3). These estimates were only slightly enhanced when BMI and perceived stress at work were left out of the fully adjusted model (results are available in supplemental material table C, http://www.sjweh.fi/index.php?page=data-repository). We found a statistically significant increase in CVD mortality among nurses working night shifts (HR 1.71, 95% CI 1.09–2.69) and a weaker, statistically non-significant increase among nurses working evening (HR 1.47, 95% CI 0.98–2.18) and rotating (HR 1.24, 95% CI 0.87–1.77) shifts in the fully adjusted model. We found no associations between cancer mortality and evening (HR 1.15, 0.95–1.40), night (HR 1.05, 95% CI 0.81–1.35), or rotating shift (HR 0.91, 95% CI 0.77–1.08) in the fully adjusted model. We found a strong positive, statistically significant association between night shift work (HR 12.0, 95% CI 3.17–45.2) and diabetes mortality and weaker associations with evening (HR 2.94, 95% CI 0.63–13.7) and rotating (HR 1.57, 95% CI 0.34–7.21) shifts. We found strong positive, statistically significant associations between mortality from Alzheimer's or dementia among nurses working evening (HR 4.28, 95% CI 1.62–11.3) and rotating (HR 5.39, 95% CI 2.35–12.3) shifts in the fully adjusted model. There was no evidence of association between working night shifts and Alzheimer's or dementia (HR 0.70, 95% CI 0.09–5.72), but this analysis was based only on a single case. Finally, we found no evidence of an increased risk in mortality from psychiatric diseases.

We found no significant associations between shift work and mortality due to any of the cancer subtypes

Table 2. Characteristics of 18 015 nurses by working shift type at baseline (1993 and 1999).

	Day		Evening		Night		Rotating		P-value [a]
	N	%	N	%	N	%	N	%	
Total	11 272	62.6	1805	10.0	980	5.4	3958	22.0	
Number of deaths [b]	934	57.8	236	14.6	151	9.3	295	18.3	
Person-years	199 327	62.9	32 245	10.2	17 662	5.6	67 410	21.3	
Body mass index (kg/m^2)									
<18.5	200	1.8	54	3.0	31	3.2	69	1.7	<0.001
18.5–24.9	7945	70.5	1308	72.5	612	62.4	2823	71.3	
25–29.9	2494	22.1	342	18.9	257	26.2	871	22.0	
≥30	633	5.6	101	5.6	80	8.2	195	4.9	
Smoking status									
Never	4260	37.8	669	37.1	298	30.4	1498	37.8	<0.001
Past	3390	30.1	471	26.1	238	24.3	1145	28.9	
Current	3622	32.1	665	36.8	444	45.3	1315	33.2	
Number of pack years [c]									
≤10	3260	28.9	460	25.5	214	21.8	1162	29.4	<0.001
11–20	1823	16.2	287	15.9	173	17.7	659	16.6	
>20	1929	17.1	389	21.6	295	30.1	639	16.1	
Alcohol consumption (drinks/week)									
0	1097	9.7	333	18.4	252	25.7	508	12.8	<0.001
1–14 (moderate)	7312	64.9	1134	62.8	523	53.4	2553	64.5	
>15 (heavy)	2863	25.4	338	18.7	205	20.9	897	22.7	
Physical activity									
Low	649	5.8	78	4.3	56	5.7	173	4.4	<0.001
High	3157	28.0	511	28.3	309	31.5	1176	29.7	
Medium	7466	66.2	1216	67.4	615	62.8	2609	65.9	
Diet									
Consume vegetables on daily basis	11 141	98.8	1773	98.2	962	98.2	3911	98.8	0.059
Consume fruit on daily basis	10 887	96.6	1711	94.8	939	95.8	3850	97.3	<0.001
Avoids fatty meat	10 363	91.9	1619	89.7	862	88.0	3626	91.6	<0.001
Self-reported pre-existing diseases									
Hypertension	1194	10.6	198	11.0	123	12.6	375	9.5	0.025
Diabetes	91	0.8	23	1.3	17	1.7	27	0.7	0.003
Myocardial infarction	26	0.2	9	0.5	5	0.5	7	0.2	0.052
Self-reported health									
Very good	5218	46.3	618	34.2	338	34.5	1820	46.0	<0.001
Good	4868	43.2	885	49.0	466	47.6	1721	43.5	
Moderate	1075	9.5	271	15.0	169	17.2	379	9.6	
Bad	100	0.9	28	1.6	7	0.7	31	0.8	
Very bad	11	0.1	3	0.2	0	0.0	7	0.2	
Working status									
Working	11 220	99.5	1797	99.6	979	99.9	3928	99.2	0.34
Homeworker	0	0.0	0	0.0	0	0.0	1	<0.1	
Retired	6	0.1	1	0.1	0	0.0	2	0.1	
Unemployed/rehabilitation	2	<0.1	1	0.1	0	0.0	1	<0.1	
Other	44	0.4	6	0.3	1	0.1	26	0.7	
Stressful work environment									
Never	141	1.3	29	1.6	41	4.2	40	1.0	<0.001
Rarely	1530	13.6	362	20.1	383	39.1	572	14.5	
Occasionally	4643	41.2	904	50.1	433	44.2	1808	45.7	
Often	3868	34.3	445	24.7	108	11.0	1292	32.6	
Almost always	1090	9.7	65	3.6	15	1.5	246	6.2	
Marital status									
Married	8602	76.3	1345	74.5	665	67.9	2864	72.4	<0.001
Separated	185	1.6	32	1.8	18	1.8	93	2.3	
Divorced	1223	10.8	214	11.9	151	15.4	506	12.8	
Single	832	7.4	126	7.0	80	8.2	367	9.3	
Widow	430	3.8	88	4.9	66	6.7	128	3.2	
Use of hormone therapy									
Never-users	8574	76.1	1293	71.6	672	68.6	3125	79.0	<0.001
Ever-users	2698	23.9	512	28.4	308	31.4	833	21.0	
Use of oral contraceptives									
Never-users	3580	31.8	723	40.1	412	42.0	1073	27.1	<0.001
Ever-users	7692	68.2	1082	59.9	568	58.0	2885	72.9	
Births									
0	1213	10.8	191	10.6	117	11.9	457	11.5	0.38
≥1	10 059	89.2	1614	89.4	863	88.1	3501	88.5	

[a] Categorical groups compared using Pearson's Chi-squared.

[b] All-cause mortality.

[c] One pack year was defined as 20 cigarettes/day/year in ever-smokers.

Table 3. Association between shift work and all-cause and cause-specific mortality among 18 015 nurses. [HR=hazard ratio; 95% CI=95% confidence intervals; ref=reference]

Mortality	Cases		Crude [a]		Adjusted [b]	
	N	%	HR	95% CI	HR	95% CI
All causes						
Day shifts (ref)	934	57.8	1.00		1.00	
Evening shifts	236	14.6	1.53	1.33–1.77	1.29	1.11–1.49
Night shifts	151	9.3	1.74	1.48–2.07	1.26	1.05–1.51
Rotating shifts	295	18.3	0.98	0.86–1.12	1.00	0.88–1.15
All cardiovascular						
Day shifts (ref)	114	52.5	1.00		1.00	
Evening shifts	33	15.2	1.74	1.18–2.57	1.47	0.98–2.18
Night shifts	26	12.0	2.42	1.58–3.71	1.71	1.09–2.69
Rotating shifts	24	20.3	1.21	0.86–1.72	1.24	0.87–1.77
All cancers						
Day shifts (ref)	578	61.2	1.00		1.00	
Evening shifts	126	13.3	1.33	1.09–1.61	1.15	0.95–1.40
Night shifts	73	7.7	1.38	1.08–1.76	1.05	0.81–1.35
Rotating shifts	168	17.8	0.89	0.75–1.06	0.91	0.77–1.08
Diabetes						
Day shifts (ref)	6	30.0	1.00		1.00	
Evening shifts	3	15.0	3.03	0.76–12.1	2.94	0.63–13.7
Night shifts	8	40.0	14.4	4.99–41.6	12.0	3.17–45.2
Rotating shifts	3	15.0	1.54	0.39–6.18	1.57	0.34–7.21
Alzheimer's and dementia						
Day shifts (ref)	10	30.3	1.00		1.00	
Evening shifts	8	24.2	4.65	1.84–11.8	4.28	1.62–11.3
Night shifts	1	3.0	0.99	0.13–7.72	0.70	0.09–5.72
Rotating shifts	14	42.4	4.79	2.12–10.8	5.39	2.35–12.3
Psychiatric diseases						
Day shifts (ref)	33	49.3	1.00		1.00	
Evening shifts	11	16.4	2.02	1.02–4.01	1.66	0.82–3.34
Night shifts	6	9.0	1.97	0.83–4.71	1.17	0.47–2.92
Rotating shifts	17	25.4	1.58	0.88–2.84	1.57	0.87–2.84

[a] Model adjusted for age.

[b] Model adjusted for age, smoking, pack-years, physical activity, body mass index (kg/m^2), alcohol consumption, diet (vegetables, fruit and fatty meat consumption), pre-existing diseases (hypertension, diabetes and myocardial infarction), self-reported health, stressful work environment, marital status, female reproductive factors (birth, use of hormone therapy and oral contraceptives).

Table 4. Association between shift work and cancer-specific mortality. [HR=hazard ratio; 95% CI=95% confidence intervals; ref=reference].

Mortality	Cases		Crude [a]		Adjusted [b]	
	N	%	HR	95% CI	HR	95% CI
Breast cancer [c]						
Day shifts (ref)	119	58.3	1.00		1.00	
Evening shifts	31	15.2	1.60	1.08–2.38	1.36	0.90 –2.03
Night shifts	16	7.8	1.50	0.89–2.53	1.20	0.70–2.08
Rotating shifts	38	18.6	0.96	0.66–1.38	0.95	0.66–1.37
Ovarian cancer [c]						
Day shifts (ref)	64	68.8	1.00		1.00	
Evening shifts	12	12.9	1.14	0.62–2.12	1.00	0.54–1.89
Night shifts	4	4.3	0.69	0.25–1.88	0.63	0.22–1.78
Rotating shifts	13	14.0	0.62	0.34–1.12	0.64	0.35–1.16
Lung cancer						
Day shifts (ref)	111	57.2	1.00		1.00	
Evening shifts	31	16.0	1.69	1.13–2.52	1.31	0.87–1.98
Night shifts	19	9.8	1.84	1.13–3.00	1.09	0.65–1.82
Rotating shifts	33	17.0	0.92	0.63–1.36	0.96	0.65–1.42
Colorectal cancer						
Day shifts (ref)	76	65.0	1.00		1.00	
Evening shifts	12	10.3	0.96	0.52–1.76	0.85	0.46–1.59
Night shifts	9	7.7	1.29	0.65–2.57	1.02	0.50–2.11
Rotating shifts	20	17.1	0.81	0.49–1.32	0.83	0.50–1.36
Pancreatic cancer						
Day shifts (ref)	45	69.2	1.00		1.00	
Evening shifts	8	12.3	1.08	0.51–2.28	0.96	0.44–2.07
Night shifts	2	3.1	0.48	0.12–1.98	0.37	0.09–1.58
Rotating shifts	10	15.4	0.69	0.35–1.37	0.67	0.34–1.36
All other cancers						
Day shifts (ref)	163	59.9	1.00		1.00	
Evening shifts	32	11.8	1.19	0.82–1.75	1.09	0.74–1.61
Night shifts	23	8.5	1.54	0.99–2.38	1.29	0.82–2.04
Rotating shifts	54	19.9	1.02	0.75–1.38	1.05	0.77–1.43

[a] Model adjusted for age.

[b] Model adjusted for age, smoking, pack-years, physical activity, body mass index (kg/m^2), alcohol consumption, diet (vegetables, fruit and fatty meat consumption), pre-existing diseases (hypertension, diabetes and myocardial infarction), self-reported health, stressful work environment, marital status, female reproductive factors (birth, use of hormone therapy and oral contraceptives).

[c] Fully adjusted analysis on breast and ovarian cancer mortality was additionally adjusted for number of births and age at first birth (N=17 919).

examined, including breast, ovarian, lung, colorectal and pancreatic cancer (table 4). When considering specific CVD (table 5), we found the strongest associations with night shift workers who had a statistically significant increased risk of dying from IHD (HR 2.30, 95% CI 1.07–4.92), and evening shift workers who had significantly increased risk of dying from other CVD (HR 2.25, 95% CI 1.18–4.31). We found positive but statistically non-significant association between working night shifts and mortality from hypertension (HR 2.35, 95% CI 0.86–6.37) and stroke (HR 1.98, 95% CI 0.82–4.27).

Discussion

We found that, compared to female nurses working day shifts, nurses working night or evening shifts had statistically significantly elevated all-cause mortality. We found a significant increase in mortality due to CVD and diabetes with night shift work. We also observed a significantly increased risk of Alzheimer's and dementia with rotating and evening shifts. There was no evidence in our study of an increased risk of overall or cause-specific cancer mortality with evening, night or rotating shift work.

Our results confirm the previous findings of Nätti et al (5) and Gu et al of an association between night shift work and all-cause mortality (6). We report a 26% increased risk for all-cause mortality among night shift compared to day shift workers, which is somewhat greater than the 11% increase in all-cause mortality reported by Gu et al among nurses who worked night shifts for ≥5 years, compared to all other schedules (6). Nätti et al reported a 125% increase in all-cause mortality among females with weekly night work as compared to those with day work (5). Notably, Nätti et al found no association with all-

Table 5. Association between shift work and cause-specific mortality. [HR=hazard ratio; 95% CI=95% confidence intervals; ref=reference]

Mortality	Cases		Crude [a]		Adjusted [b]	
	N	%	HR	95% CI	HR	95% CI
Ischemic heart disease						
Day shifts (ref)	29	46.0	1.00		1.00	
Evening shifts	11	17.5	2.30	1.15–4.60	1.71	0.84–3.50
Night shifts	11	17.5	4.10	2.05–8.22	2.30	1.07–4.92
Rotating shifts	12	19.1	1.28	0.65–2.51	1.22	0.61–2.41
Hypertension						
Day shifts (ref)	19	47.5	1.00		1.00	
Evening shifts	5	12.5	1.57	0.59–4.22	1.60	0.57–4.51
Night shifts	6	15.0	3.30	1.32–8.28	2.35	0.86–6.37
Rotating shifts	10	25.0	1.68	0.78–3.62	2.04	0.92–4.50
Stroke						
Day shifts (ref)	42	56.8	1.00		1.00	
Evening shifts	7	9.5	1.00	0.45–2.23	0.91	0.40–2.05
Night shifts	9	12.2	2.27	1.10–4.67	1.98	0.92–4.27
Rotating shifts	16	2.6	1.20	0.68–2.14	1.24	0.70–2.22
Other cardiovascular						
Day shifts (ref)	33	53.2	1.00		1.00	
Evening shifts	14	22.6	2.55	1.37–4.77	2.25	1.18–4.31
Night shifts	4	6.5	1.29	0.46–3.64	0.95	0.32–2.80
Rotating shifts	11	17.7	1.05	0.53–2.08	1.19	0.59–2.38

[a] Model adjusted for age.

[b] Model adjusted for age, smoking, pack-years, physical activity, body mass index (kg/m^2), alcohol consumption, diet (vegetables, fruit and fatty meat consumption), pre-existing diseases (hypertension, diabetes and myocardial infarction), self-reported health, stressful work environment, marital status, female reproductive factors (birth, use of hormone therapy, and oral contraceptives).

cause mortality among male night shift workers, which may suggest different susceptibility by gender. Nätti et al's observed gender differences were consistent with Åkerstedt et al's results, where a significant association with mortality was limited to female white-collar night shift workers, whereas none was found among male night workers or female blue-collar workers (10). Gender variation in susceptibility to night work may also explain why our results conflict with studies based on male participants (3, 4, 7, 8, 12).

Work schedule is dependent on age, and it has previously been documented that nurses in younger age groups are more likely to work in rotating shifts, whereas nurses >40 years more often work in day or evening shifts (30). However, 90% of nurses working in Denmark have worked night shifts at some point, typically early in their career after completing their training. We found a similar increase in all-cause mortality for night (26%) and evening (29%) shift workers. This might be explained by the fact that a large number of nurses who worked evening shifts at the time of cohort recruitment have worked night shifts earlier in their career. Another possible explanation for the increased mortality among evening workers might be that this work schedule is associated with an increase in social stress and more work-family related conflicts. Furthermore, other unmeasured potentially confounding variables such as weekly working hours could explain these findings.

The lack of association between rotating shift work and all-cause mortality is possibly explained by the fact that rotating shift work involves day, evening and night shifts or only day and evening shifts and few night shifts in a sequence, probably resulting in minor circadian disturbance. A Danish report on occupational health among nurses from the Danish Nurses Organization, reveals that 43% of nurses aged 20–29 years work rotating 3-shifts, while this attenuates to 20% among nurses aged 40–49 years and 12% among those aged 50–59 years, indicating that 3-shift rotating work is more prevalent early in the career, and thus making it less prevalent in our cohort (30). Alternatively, the lack of association between rotating shifts and all-cause mortality might be explained if a high proportion of previous rotating shift workers changed to day shifts positions. This could result in increased mortality rate among day workers and an underestimation of the impact of shift work (30).

The IARC has classified shift work that involves circadian disruption as "probably carcinogenic to humans" (group 2A) due to increased risk of breast cancer incidence among women (31). We found no association between shift work and all-cancer mortality, in agreement with Gu et al (6), and in contrast to Nätti et al (5). Furthermore, no evidence of an increase in mortality related to shift work was found for any specific cancers including cancer of the breast, which is in agreement with some of the previous studies (6, 7, 17). However our findings are in conflict with increased mortality due to ovarian cancer reported by Carter et al (19) and increased mortality due to lung cancer (≥15 years of rotating night shift work) and breast cancer reported by Gu et al (6). Gu et al. found an association with breast cancer mortality only among those working night shifts ≥30 years (HR 1.47, 95% CI 0.94–2.32), and none with more recent exposures, suggesting the relevance of early exposure for the development for breast cancer (6). This in line with Menegaux et al (32) who found the strongest risk of developing breast cancer among women who worked night shifts for >4 years before their first full-term pregnancy, a period where mammary glands are not completely differentiated and possibly more susceptible to circadian disruption effects. Thus lack of effects of shift work on breast cancer mortality in our study may be due, at least in part, to lack of information on shift work duration and shift work schedules, before the first childbirth.

We found a 71% increase in CVD mortality among nurses working night shifts, which was considerably higher than the 19% and 23% detected in American nurses with ≥5 and ≥15 years of night shift work, respectively (6). We furthermore found the highest increased rate (130%) related to night shift work for IHD mortality, which is consistent with some studies (6, 33, 34),

however is inconsistent with others (8, 35, 36). Inconsistencies are likely explained by differences in study populations in terms of the gender and age of included subjects. Knutsson et al's case–control study of MI incidence detected associations with both male and female shift workers, but found substantially higher risk [odds ratio (OR) 3.0, 95% CI 1.4–6.5] among females aged 45–55 years than males of the same age (OR 1.6, 95% C 1.1–2.4) (37). Since the majority (~80%) of participants included were 44–55 years of age at the time of recruitment, a large proportion of the shift-working nurses in our study might, based on the results of Knutsson et al, be at particularly high risk of developing MI due to shift work, possibly explaining strong effects observed in our study and the lack of association between shift work and IHD mortality in most studies based on male participants (8, 35, 36). We also found statistically non-significant associations between night shift work and risk of dying from hypertension and stroke and increased risk of dying from other CVD among evening shift workers. These findings agree with Vyas et al's recent meta-analysis that has linked shift work to increases in the incidence of various vascular events including, MI (23%), ischemic stroke (5%) and coronary events (24%) (20). Disruption of circadian rhythms is thought to be the plausible mechanisms linking shift work with CVD through multifactorial pathways (38, 39), involving weight gain, physical inactivity, development of type II diabetes, and other pathways (38).

The highest rate ratio associated with night shift work in this study was observed for diabetes mortality, however, the results are based on a limited number of diabetes deaths (N=8) and therefore somewhat unstable. Our results are considerably stronger than the effect in the Karlsson et al (12) study of Swedish male workers from the pulp and paper industry (HR 1.24, 95% CI 0.91–1.70). Karlsson et al included males enrolled at age 10 in 1952 and used shift work as a dichotomized exposure (all shift versus day worker), but, on the other hand, included data on duration of shift work and found strong indication of a positive dose–response relationship with diabetes mortality. We have recently reported a strong significant association between night shift work and diabetes incidence (HR 1.58, 95% CI 1.25–1.99) in the DNC (12). Results based on the Nurses' Health Study I and II (40) and the Black Women's Health Study (41) also detected an association between night shift work and diabetes incidence.

We provided novel results of the strong increase in mortality from Alzheimer's and dementia among nurses working evening and rotating shifts. To our knowledge this is the first study to report such an association. However, our results are based on a limited number of cases (33 deaths in total), and further studies of this issue are clearly warranted. Studies have put forth plausible biological mechanisms suggesting that sleep disturbance results in substantial detrimental cognitive effects (26). Unlike for all-cause mortality where no effect of rotating shifts was observed, we found the strongest associations for Alzheimer's and dementia among rotating shifts workers. This result may suggest relevance of other mechanisms, possibly stress-related for Alzheimer's and dementia than for all-cause mortality where circadian disruption may be more relevant. Furthermore, recent studies have shown an association between short sleep duration with greater β-amyloid (Aβ) burden, a biomarker of Alzheimer's progression (25), and that better sleep consolidation substantially attenuated the negative effects of the apolipoprotein E ε4 allele, a common genetic risk factor for Alzheimer's (24).

Strengths and limitations

A major strength of this study is the utilization of a nationwide prospective cohort of 18 015 female nurses, with detailed information on work schedules (night, evening, rotating, day), lifestyle, BMI, history of diseases, and reproductive factors at the time of cohort enrolment, and long follow-up for overall and cause-specific mortality in a national registry. In contrast to the commonly used shift work definition as a dichotomous exposure, typically comparing day to shift workers and combining evening, night and rotating shifts, in this study we were able to separate effect of night, evening and rotating shift in comparison to day shift work for the first time in a study of mortality. We excluded 10 716 (~37%) of the participants due to missing values. A majority of the participants (6721) were excluded because the question about work schedule was aimed at nurses working (74%) at the time of recruitment only. We found that the age-adjusted mortality was significantly higher among excluded nurses (HR 4.07, 95% CI 3.84–4.31) compared to included nurses, as expected since excluded nurses were on average 10 years older (mean age 60.0 years versus 50.2 years) at the time of recruitment. This is explained by the fact that a majority of excluded nurses were retired or on sick leave or disability retirement at the time of recruitment, and were therefore not included in the assessment of shift work. We found no major differences in lifestyle, BMI, or other characteristics between included and excluded nurses (supplemental material tables A and B, http://www.sjweh.fi/index.php?page=data-repository).

A major limitation of this study is the lack of data on intensity and duration of shift work in terms of the number of shifts per week or month, number of working hours per shift, and number of years working in shift work. The exposure was only assessed at baseline with no follow-up on changes in work schedule, potentially introducing exposure misclassification. However the nurses were followed from age 44 years when in general it is less likely for nurses to change work schedule than

earlier in their careers. We also lacked information on duration of recovery periods and work schedules early in their career (from completion of professional training to cohort recruitment) and information on different types of rotating shift schedule, particularly whether or not rotating shifts involved night shifts. Another limitation is the small number of deaths for some of the examined outcomes (eg, diabetes and Alzheimer's and dementia), resulting in wide confidence intervals, and our findings need to be replicated in larger studies. Furthermore, the registration of underlying and contributory causes of death relies entirely on the physician responsible for completing the death certificate, without central validation, which together with increasing diagnostic facilities influence the accuracy and correctness of the register and changes in mortality rates over the years (29).

Healthcare professionals are generally considered to be healthier than the general population, and a "healthy worker effect" might have biased our results. Nurses participating in this cohort have been found to be healthier than Danish women in general, as they smoked less and had higher levels of physical activity, but on average they consumed more alcohol.(27, 42) However, there were no major health differences between nurses and the rest of Danish female population in use of healthcare and disease occurrence.(27, 42)

In conclusion, we found evidence of an increased all-cause mortality risk among female nurses working in night or evening shifts, compared to those working in day shifts. We further found evidence of increased mortality due to CVD and diabetes, and Alzheimer's and dementia, while there was no evidence of an increased risk in mortality from psychiatric diseases and overall or cause specific cancer. Additional studies of mortality among shift workers are warranted.

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The authors declare no conflicts of interest.

Ethical approval

Relevant Danish ethical committees and Danish Data Protection Agency approved this study (j.nr. 2015-41-4307), and participants provided written informed consent at recruitment.

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