Original Investigation

Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease Among Women

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IMPORTANCE Prospective studies linking shift work to coronary heart disease (CHD) have been inconsistent and limited by short follow-up.

OBJECTIVE To determine whether rotating night shift work is associated with CHD risk.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study of 189 158 initially healthy women followed up over 24 years in the Nurses' Health Studies (NHS [1988-2012]: N = 73 623 and NHS2 [1989-2013]: N = 115 535).

EXPOSURES Lifetime history of rotating night shift work (≥3 night shifts per month in addition to day and evening shifts) at baseline (updated every 2 to 4 years in the NHS2).

MAIN OUTCOMES AND MEASURES Incident CHD; ie, nonfatal myocardial infarction, CHD death, angiogram-confirmed angina pectoris, coronary artery bypass graft surgery, stents, and angioplasty.

RESULTS During follow-up, 7303 incident CHD cases occurred in the NHS (mean age at baseline, 54.5 years) and 3519 in the NHS2 (mean age, 34.8 years). In multivariable-adjusted Cox proportional hazards models, increasing years of baseline rotating night shift work was associated with significantly higher CHD risk in both cohorts. In the NHS, the association between duration of shift work and CHD was stronger in the first half of follow-up than in the second half (P=.02 for interaction), suggesting waning risk after cessation of shift work. Longer time since quitting shift work was associated with decreased CHD risk among ever shift workers in the NHS2 (P<.001 for trend).

	Baseline History of Rotating Night Shift Work				*P* Value for Trend
	None	<5 y	5-9 y	≥10 y	
NHS cohort					
CHD incidence rate[a]	425.5	435.1	525.7	596.9	
HR (95% CI)[b]	1 [Reference]	1.02 (0.97-1.08)	1.12 (1.02-1.22)	1.18 (1.10-1.26)	<.001
First half of follow-up					
CHD incidence rate[a]	367.3	382.4	483.1	494.4	
HR (95% CI)[b]	1 [Reference]	1.10 (1.01-1.21)	1.19 (1.03-1.39)	1.27 (1.13-1.42)	<.001
Second half of follow-up					
CHD incidence rate[a]	436.6	424.8	520.7	556.2	
HR (95% CI)[b]	1 [Reference]	0.98 (0.92-1.05)	1.08 (0.96-1.21)	1.13 (1.04-1.24)	.004
NHS2 cohort					
CHD incidence rate[a]	122.6	130.6	151.6	178.0	
HR (95% CI)[b]	1 [Reference]	1.05 (0.97-1.13)	1.12 (0.99-1.26)	1.15 (1.01-1.32)	.01

[a] Age-adjusted rates per 100 000 person-years.
[b] Multivariable-adjusted hazard ratio (HR).

CONCLUSIONS AND RELEVANCE Among women who worked as registered nurses, longer duration of rotating night shift work was associated with a statistically significant but small absolute increase in CHD risk. Further research is needed to explore whether the association is related to specific work hours and individual characteristics.

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Societal and economic demands push toward an increase of employees' 24-hour availability in health care settings as well as in service and security industries. The resulting disruption of social and biological rhythms, occurring especially during shift work, has been hypothesized to increase chronic disease risk,[1-5] and suggestive evidence supports an association between shift work and coronary heart disease (CHD), metabolic disorders, and cancer.[6]

In 1995, Kawachi et al[7] examined the association between rotating night shift work and CHD in the Nurses' Health Study (NHS) over 4 years of follow-up and reported a 51% significant increase in CHD risk (nonfatal myocardial infarction [MI] and CHD death) among women with more than 6 years of rotating night shift work after multivariable adjustment (incidence rate per 100 000 person-years, 156.1 compared with 75.4 among women who never worked night shifts). A recent systematic meta-analysis reported a 24% elevated CHD risk associated with most types of shift work but noted significant heterogeneity in exposure assessment and study designs across studies.[8] The present study reassessed the association of rotating night shift work and coronary health in the Nurses' Health Studies (NHS and NHS2) with 24 years of follow-up and examined manifestations of CHD (angiogram-confirmed angina pectoris, coronary artery stents, angioplasty, and coronary artery bypass graft [CABG] surgery), in addition to nonfatal MI and CHD death. Additionally, possible differences in this association over time, including effects of time since quitting shift work, were explored. The study also examined the excess risk of CHD associated with shift work among women without diabetes, hypertension, or hypercholesterolemia—potential comorbid mediators of CHD.

Methods

Study Population

The NHS and NHS2 are ongoing, prospective cohort studies. The NHS began in 1976 when 121 701 female registered US nurses aged 30 to 55 years responded to a baseline questionnaire.[9] The NHS2 started in 1989 and included 116 430 female registered US nurses aged 25 to 42 years. In both cohorts, biennial follow-up questionnaires have been mailed to update information on medical history, lifestyle factors, and newly diagnosed diseases. Follow-up rates were high in both cohorts, with approximately 90% participation at each 2-year cycle. This study was reviewed and approved by the Brigham and Women's Hospital Institutional Review Board; completion of the self-administered questionnaire was considered informed consent, so the requirement for oral or written consent was waived.

Rotating Night Shift Work Assessment

In the NHS, lifetime years of exposure to rotating night shift work (defined as ≥3 night shifts per month, in addition to day and evening shifts) was queried once, in 1988. In the NHS2, women indicated in 1989 how many years of rotating night shift work they had worked, with updates in 1991, 1993, 1997, 2001, 2005, and 2007; retrospective assessments for shift work in 1995, 1999, and 2003 were included on the 2001 and 2005 questionnaires, respectively. The analyses used baseline assessments of lifetime shift work history in each cohort (1988 for NHS and 1989 for NHS2), as well as cumulative shift work exposure through 2007 in the NHS2. In all analyses, night shift work information was carried forward for 1 questionnaire cycle in the case of missing data.

Ascertainment of CHD

On baseline and follow-up questionnaires, participants were asked to report physician-diagnosed CHD events. Those who reported nonfatal MI were asked for medical record access so that exposure-blinded physicians could confirm self-reported nonfatal MI. Nonfatal MI was confirmed using the World Health Organization criteria, which required diagnostic electrocardiographic findings or elevated enzyme levels in addition to typical symptoms.[10] Participant deaths were identified through the National Death Index, next of kin, or postal authorities, with primary cause of death being determined by autopsy reports, hospital records, and death certificates. The primary outcome was incident CHD, including self-reported cases of CABG surgery, angina pectoris (confirmed by angiogram), angioplasty, and coronary artery stents, in addition to nonfatal MI and CHD death (including fatal MI), whichever came first. Secondary analyses were restricted to nonfatal MI and CHD death.

Covariate Assessment

In both cohorts, biennial questionnaires were used to collect information on medical history, anthropometric data, diet, and lifestyle. Most variables were updated biennially from baseline onward; physical activity and dietary data were obtained approximately every 4 years. Dietary habits were assessed using a semiquantitative, validated food frequency questionnaire[11] calculating the Alternative Healthy Eating Index, which has previously been found to be a reliable predictor of CHD in these cohorts.[12] Parity was updated until 1996 and 2009 for the NHS and NHS2, respectively, and subsequently carried forward. Participants' husbands' educational attainment (a proxy for socioeconomic status assessed in 1992 in NHS and in 1999 in NHS2), family history of MI before age 60 years (1976 and 1984 in NHS and 1989, 1997, and 2001 in NHS2), and race (2004 in NHS and 1989 and 2005 in NHS2) were not updated throughout follow-up. Usual sleep duration assessed in 1986, 2000, and 2008 (NHS) and 2001 (NHS2), and social support (assessed by asking whether participants had a confidant) in 1992, 2000, 2004, and 2008 (NHS) and in 1993 (NHS2) were not regularly updated throughout follow-up.

Statistical Analyses

Age- and multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals across rotating night shift work categories (none, <5, 5-9, and ≥10 years). Women with no history of rotating night shift work comprised the reference category in all analyses. Calculations of *P* values for trend were based on the midpoint of rotating night shift work categories, with the highest category conservatively set to 10; the reported *P* value was based on the Wald test. The proportional hazards assumption was tested by including an interaction of shift work

(ie, midpoint of categories) by time in all models, and its significance was evaluated using the Wald statistic. In sensitivity analyses, the outcome was restricted to nonfatal MI and CHD death. Additional sensitivity analyses were restricted to participants with no baseline history of major comorbidities potentially mediating CHD (ie, diabetes, hypertension, and hypercholesterolemia) and censored women who reported any of these conditions throughout follow-up.

The following cardiovascular disease risk factors were included in multivariable-adjusted models: family history of MI before age 60 years, diet quality (Alternative Healthy Eating Index,[12] without the alcohol and multivitamin components, in quintiles), physical activity (metabolic equivalent task-hours per week, in quintiles), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared: <25, 25-29, 30-35, or >35), cumulative pack-years smoked (continuous), alcohol intake (none, 0.1-5, 5.1-10, 10.1-20, or >20 g/d), parity (nulliparous, 1, 2, or ≥3 children), menopausal status (premenopausal or postmenopausal), hormone therapy (premenopausal, ever, or never), race (white, black, or other), husband's highest educational level (high school diploma or less, college degree, or graduate school level or similar), multivitamin use (yes or no), acetaminophen use (yes or no), nonsteroidal anti-inflammatory drug use (yes or no), aspirin use (yes or no), hypertension (yes or no), diabetes (yes or no), and hypercholesterolemia (yes or no). In additional analyses, models were adjusted for sleep duration (<6, 6-7, 8-9, or ≥10 hours per day) and social support (yes or no). Dummy variables were used to indicate missing covariate values. For missing information on pack-years of smoking, the median among smokers was imputed; in the case of missing BMI, information was carried forward once. On average, 9.5% of covariate information was missing across 24 years of follow-up.

In the NHS2, analyses also examined the association between cumulative time since quitting rotating night shift work (never, current, <12, 12-24, or >24 years) and CHD risk. Time since quitting rotating night shift work was estimated based on lifetime reports of exposure in 1989 and updated shift work information throughout follow-up. If women reported rotating night shifts at baseline only, time since quitting shift work was estimated by subtracting 21 years (assumed age at starting shift work) and the lower bound of the categorically reported duration of rotating night shift work from their age in 1989.

In additional secondary analyses, potential effect modification by BMI (<25, 25-30, or >30) was examined, adjusting continuously for BMI within each stratum. To evaluate potential interactions, the log likelihood ratio test was used to compare models with and without cross-product interaction terms; corresponding *P* values were based on χ^2 statistics.

The a priori hypothesis was that rotating night shift work increased CHD risk, and all secondary analyses were preplanned. Analyses were conducted with SAS software, version 9.4 (SAS Institute Inc) with a 2-sided significance threshold of $P < .05$.

Results

A total of 103 525 NHS participants answered the 1988 questionnaire. Of these, women with CHD, stroke, or cancer (n = 14 065) and those who did not answer the shift work question in 1988 (n = 15 837) were excluded, leaving 73 623 women for analysis. In the NHS2, 116 430 women answered the baseline questionnaire (1989), of whom 895 reported stroke or CHD prior to baseline, so that after the same exclusions, 115 535 women were left for analysis. For the NHS2 analysis with updated shift work information, women who did not answer shift work questions for 2 consecutive cycles (on average, 8.7% per cycle) were censored. Women were excluded from further follow-up after any self-reported stroke, incident CHD, or death.

During 24 years of follow-up, a total of 10 822 incident CHD cases were observed (7303 in NHS and 3519 in the younger NHS2). **Table 1** describes age and age-adjusted (within-cohort) characteristics of the study population across categories of lifetime years of rotating night shift work at baseline. Compared with women in the NHS, women in the NHS2 were younger, more likely to be nulliparous, had slightly lower alcohol consumption, reported fewer pack-years of smoking, had fewer comorbid conditions, and took fewer medications and multivitamin supplements. With increasing duration of rotating night shift work, women were heavier in both cohorts. Also, in the NHS, a lower proportion of women had husbands with graduate-level education across increasing categories of shift work, while pack-years of smoking and self-reports of hypertension increased; in the NHS2, a greater proportion of nulliparous women and acetaminophen users were observed with increasing duration of rotating night shift work.

Compared with women without a history of rotating night shift work (incidence rates, 425.5 and 122.6 per 100 000 person-years in the NHS and NHS2, respectively), women who worked less than 5 years of shift work at baseline did not have a significantly increased CHD risk in age-adjusted analyses (**Table 2** and **Table 3**), but there was a significant association between longer durations of shift work and CHD risk (in the NHS: incidence rate per 100 000 person-years for 5-9 years, 525.7; HR, 1.21 [95% CI, 1.11-1.33]; incidence rate for ≥10 years, 596.9; HR, 1.36 [95% CI, 1.27-1.46]; *P*<.001 for trend; in the NHS2: incidence rate for 5-9 years, 151.6; HR, 1.22 [95% CI, 1.08-1.38]; incidence rate for ≥10 years, 178.0; HR, 1.34 [95% CI, 1.17-1.53]; *P*<.001 for trend).

Multivariable adjustment for known CHD risk factors attenuated these estimates, but the elevated risk observed for 5 years or more of shift work persisted in the NHS (multivariable HR for 5-9 years, 1.12 [95% CI, 1.02-1.22]; multivariable HR for ≥10 years, 1.18 [95% CI, 1.10-1.26]; *P*<.001 for trend), and for 10 years or more of shift work in the NHS2 (multivariable HR for 5-9 years, 1.12 [95% CI, 0.99-1.26]; multivariable HR for ≥10 years, 1.15 [95% CI, 1.01-1.32]; *P* = .01 for trend).

In the NHS, there was a significant interaction between rotating night shift work exposure and time (by 2-year period, *P*<.001 for interaction) (Table 2), suggesting that CHD risk associated with shift work changes over time. During the first half of follow-up, higher effect estimates and significantly elevated risks also were observed with shorter durations of shift work exposure (incidence rate per 100 000 person-years for <5 years, 382.4; multivariable HR, 1.10 [95%

Table 1. Age and Age-Adjusted Characteristics of Participating Women at Baseline by Rotating Night Shift Work History[a]

Characteristics	Rotating Night Shift Work Exposure (≥3 Night Shifts Per Month)							
	NHS (1988)				NHS2 (1989)			
	None (n=30 012)	<5 y (n=30 122)	5-9 y (n=4955)	≥10 y (n=8534)	None (n=43 657)	<5 y (n=56 179)	5-9 y (n=9866)	≥10 y (n=5833)
Age, mean (SD), y	54.0 (7.1)	54.3 (7.1)	54.9 (7.1)	56.2 (6.9)	34.8 (4.7)	34.5 (4.7)	35.1 (4.2)	37.1 (3.6)
White race, No. (%)	29 390 (98)	29 424 (98)	4832 (98)	8250 (97)	42 075 (96)	53 501 (95)	9337 (95)	5479 (95)
Parity, No. (%)								
Nulliparous	1434 (5)	1795 (6)	351 (7)	539 (6)	12 111 (28)	17 814 (31)	3440 (36)	1795 (37)
1 or 2 children	10 415 (34)	10 650 (35)	1761 (36)	2853 (35)	23 249 (53)	28 704 (51)	4889 (50)	2926 (48)
≥3 children	17 750 (60)	17 211 (57)	2743 (55)	4956 (57)	8290 (19)	9653 (18)	1536 (15)	1109 (16)
Parental history of MI at age <60 y, No. (%)	4893 (16)	5081 (17)	879 (18)	1516 (18)	6105 (14)	8294 (15)	1670 (17)	1011 (16)
Body mass index, mean (SD)[b]	25.2 (4.8)	25.4 (4.8)	26.0 (5.3)	26.6 (5.4)	23.9 (4.9)	24.0 (5.0)	24.8 (5.5)	25.1 (5.8)
No. (%)								
<25	18 206 (61)	17 910 (59)	2683 (54)	4242 (50)	31 400 (72)	39 851 (71)	6365 (65)	3420 (62)
25-29.9	7926 (27)	8107 (27)	1455 (29)	2559 (30)	7693 (18)	10 300 (18)	2068 (21)	1330 (22)
30-34.9	2645 (9)	2877 (10)	545 (11)	1116 (13)	2837 (7)	3723 (7)	853 (9)	606 (9)
≥35	1235 (4)	1228 (4)	272 (6)	617 (7)	1727 (4)	2305 (4)	580 (6)	477 (7)
Pack-years of smoking, median (IQR)[c]	18 (7-34)	18 (6-34)	20 (7-35)	24 (10-39)	10 (5-16)	9 (5-16)	10 (5-17)	11 (6-19)
Husband holds graduate school degree, No. (%)	5841 (19)	6346 (21)	840 (17)	1028 (12)	9351 (21)	13 810 (25)	2079 (21)	1090 (18)
Alcohol intake, median (IQR), g/d[d]	1.8 (0-7.6)	1.9 (0-8.3)	1.8 (0-7.3)	1.1 (0-6.2)	0.9 (0-3.1)	0.9 (0-3.7)	0.9 (0-3.6)	0.9 (0-2.9)
Alternative Healthy Eating Index score (2010), mean (SD)[e]	45.7 (10.5)	46.0 (10.4)	46.0 (10.3)	45.3 (10.1)	43.6 (10.5)	44.3 (10.5)	44.2 (10.4)	44.1 (10.3)
Physical activity, median (IQR), MET-hours/wk[f]	7.9 (2.9-20.2)	9.1 (3.4-20.9)	9.0 (3.4-21.5)	8.4 (3.2-21.5)	12.3 (4.7-27.4)	14.6 (5.5-31.6)	15.1 (5.8-33.3)	14.2 (5.2-32.1)
Multivitamin use, No. (%)	18 518 (62)	19 011 (63)	3148 (64)	5325 (62)	23 704 (54)	30 053 (54)	5254 (53)	3242 (55)
Aspirin use, No. (%)	18 482 (62)	19 105 (63)	3122 (63)	5374 (63)	4747 (11)	6119 (11)	1195 (12)	827 (13)
NSAID use, No. (%)	9537 (31)	9680 (32)	1575 (32)	2728 (33)	7775 (18)	10 986 (20)	2206 (22)	1409 (22)
Acetaminophen use, No. (%)[g]	11 110 (37)	11 315 (37)	1849 (38)	3204 (39)	9229 (21)	12 370 (22)	2292 (23)	1529 (26)
Postmenopausal, No. (%)	20 735 (71)	21 254 (71)	3674 (72)	6866 (74)	965 (2)	1271 (2)	247 (2)	238 (3)
Current hormone therapy, No. (%)	6833 (23)	7059 (24)	1122 (22)	1868 (21)	997 (2)	1263 (2)	246 (2)	236 (3)
Self-reported hypertension, No. (%)	7464 (25)	7641 (26)	1448 (29)	2781 (30)	2270 (5)	2938 (5)	627 (6)	460 (7)
Self-reported diabetes, No. (%)	1048 (4)	995 (3)	221 (4)	507 (6)	396 (1)	402 (1)	74 (1)	68 (1)
Self-reported hypercholesterolemia, No. (%)	6683 (23)	6837 (23)	1171 (23)	2781 (24)	4493 (10)	5809 (10)	1100 (11)	722 (11)
Usual sleep duration, No. (%), h[h]								
≤6	6978 (23)	7506 (25)	1427 (29)	2901 (34)	8939 (20)	12 230 (22)	2542 (26)	1670 (28)
7	11 299 (38)	11 353 (38)	1770 (36)	2609 (31)	13 835 (32)	17 397 (31)	2779 (28)	1552 (26)
8-9	7661 (26)	7358 (24)	1044 (21)	1709 (19)	9593 (22)	11 178 (20)	1680 (17)	892 (16)
≥10	157 (1)	132 (0)	24 (0)	56 (1)	245 (1)	322 (1)	52 (1)	37 (1)
Social support, No. (%)[i]	22 288 (94)	22 667 (94)	3617 (93)	6019 (94)	31 370 (94)	39 389 (95)	6822 (95)	3930 (94)

Abbreviations: IQR, interquartile range; MET, metabolic equivalent task; MI, myocardial infarction; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug.

[a] Numbers that do not add up to 100% are attributable to missing data.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Cumulative among smokers.

[d] Assessed in 1986 for the NHS and in 1991 for the NHS2.

[e] Assessed in 1986 for the NHS and in 1991 for the NHS2. Higher scores reflect a healthier diet.[12]

[f] Weekly energy expenditure in MET-hours from recreational and leisure time activities.

[g] Assessed in 1990 for the NHS and in 1989 for the NHS2.

[h] Assessed in 1986 for the NHS and in 2001 for the NHS2.

[i] Assessed in 1992 for the NHS and in 1993 for the NHS2.

CI, 1.01-1.21]; incidence rate for 5-9 years, 483.1; multivariable HR, 1.19 [95% CI, 1.03-1.39]; incidence rate for ≥10 years, 494.4; multivariable HR, 1.27 [95% CI, 1.13-1.42]; $P < .001$ for trend and $P = .02$ for interaction for first vs second half of follow-up). In the second half of follow-up, compared with women who never worked rotating night shifts (incidence

Table 2. Shift Work and Risk of Coronary Heart Disease in the NHS[a]

Cohort	Baseline History of Rotating Night Shift Work[b] None	<5 y	5-9 y	≥10 y	*P* Value for Trend[c]	*P* Value for Interaction, Shift Work × Time[d]
Overall NHS, 1988 to 2012						
Cases/person-years	2739/643 774	2857/644 857	568/103 574	1139/173 571		
Incidence rate per 100 000 person-years (95% CI)[e]	425.5 (383.9-467.1)	435.1 (392.8-477.5)	525.7 (410.4-641.1)	596.9 (502.1-691.7)		
Age-adjusted model, HR (95% CI)	1 [Reference]	1.02 (0.96-1.07)	1.21 (1.11-1.33)	1.36 (1.27-1.46)	<.001	
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	1.02 (0.97-1.08)	1.12 (1.02-1.22)	1.18 (1.10-1.26)	<.001	<.001
First vs second half of follow-up						.02
June 1988 to May 2000						
Cases/person-years	915/351 568	1021/352 490	213/57 612	455/97 899		
Incidence rate per 100 000 person-years (95% CI)[e]	367.3 (302.4-432.3)	382.4 (316.8-448.1)	483.1 (306.6-659.7)	494.4 (370.1-618.8)		
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	1.10 (1.01-1.21)	1.19 (1.03-1.39)	1.27 (1.13-1.42)	<.001	.03
June 2000 to May 2012						
Cases/person-years	1824/305 036	1836/305 297	355/48 238	684/79 819		
Incidence rate per 100 000 person-years (95% CI)[e]	436.6 (367.8-505.4)	424.8 (361.8-487.7)	520.7 (377.1-664.3)	556.2 (414.2-754.3)		
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	0.98 (0.92-1.05)	1.08 (0.96-1.21)	1.13 (1.04-1.24)	.004	.08
Restricted to myocardial infarction and coronary heart disease death						
June 1988 to May 2000						
Cases/person-years	443/353 659	491/354 846	117/58 026	226/99 022		
Incidence rate per 100 000 person-years (95% CI)[e]	173.0 (128.3-217.8)	182.3 (137.2-227.4)	276.2 (142.6-409.9)	236.5 (151.8-321.3)		
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	1.12 (0.99-1.28)	1.35 (1.10-1.66)	1.29 (1.09-1.51)	.001	.19
June 2000 to May 2012						
Cases/person-years	444/316 989	428/318 083	65/50 714	176/84 689		
Incidence rate per 100 000 person-years (95% CI)[e]	106.6 (73.1-140.0)	92.3 (69.1-115.5)	101.5 (36.4-166.5)	133.3 (76.4-190.1)		
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	0.95 (0.83-1.09)	0.77 (0.60-1.00)	1.09 (0.91-1.30)	.84	.56

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study.

[a] A total of 7303 coronary heart disease cases (ie, nonfatal myocardial infarction, coronary heart disease–attributed death, angiogram-confirmed angina pectoris, angioplasty, coronary artery bypass graft surgery, and coronary artery stents) occurred during 24 years of follow-up in the NHS (N = 73 623).

[b] Assessed in 1988.

[c] Based on category midpoints, except for ≥10 years, for which the midpoint was set to 10 years.

[d] Based on the interaction between shift work category midpoints (except for ≥10 years, for which the midpoint was set to 10 years) and time (in 2-year cycles).

[e] Incidence rates and 95% CIs are adjusted to the age distribution of women who reported no history of rotating night shift work, separately for each cohort.

[f] Multivariable-adjusted model included age, physical activity (metabolic equivalent task–hours per week, in quintiles), diet (Alternative Healthy Eating Index score,[12] in quintiles), alcohol consumption (none, 0.1-5, 5.1-10, 10.1-20, or >20 g/d), pack-years of smoking (continuous), parental history of myocardial infarction prior to age 60 years (yes or no), menopausal status (premenopausal vs postmenopausal), parity (nulliparous, 1 child, 2 children, or ≥3 children), hormone therapy (ever, never, or premenopausal), multivitamin use (yes or no), acetaminophen use (yes or no), nonsteroidal anti-inflammatory drug use (yes or no), aspirin use (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), diabetes (yes or no), body mass index (<25, 25-29.9, 30-34.9, or ≥35), race (white, black, or other), and husband's highest educational level (up to high school diploma, college degree, or graduate school or similar).

rate per 100 000 person-years, 436.6), only those who worked 10 years or more of shift work had a significantly elevated CHD risk (incidence rate, 556.2; multivariable HR, 1.13 [95% CI, 1.04-1.24]; *P* = .004 for trend). The association between shift work and CHD risk was not significant in the last 4 years of follow-up (2008-2012; incidence rate for <5 years, 219.9; multivariable HR, 0.85 [95% CI, 0.70-1.03]; incidence rate for 5-9 years, 247.2; multivariable HR, 0.88 [95% CI, 0.62-1.26]; incidence rate for ≥10 years, 306.3; multivariable HR, 1.04 [95% CI, 0.80-1.35]; *P* = .94 for trend) (eTable 1 in the Supplement).

All categories of rotating night shift work showed a significantly elevated CHD risk when shift work history was cumulatively updated in the NHS2 (incidence rate per 100 000 person-years for <5 years, 137.4; multivariable HR, 1.12 [95% CI, 1.01-1.24]; incidence rate for 5-9 years, 161.9;

Table 3. Shift Work and Risk of Coronary Heart Disease in the NHS2[a]

Cohort	Rotating Night Shift Work Exposure				*P* Value for Trend[b]	*P* Value for Interaction, Shift Work × Time[c]
	None	<5 y	5-9 y	≥10 y		
Baseline history of shift work[d]						
Cases/person-years	1236/1 007 860	1673/1 296 585	347/226 580	263/132 971		
Incidence rate per 100 000 person-years (95% CI)[e]	122.6 (105.0-140.3)	130.6 (114.5-146.7)	151.6 (109.2-194.0)	178.0 (123.0-234.0)		
Age-adjusted model, HR (95% CI)	1 [Reference]	1.06 (0.99-1.14)	1.22 (1.08-1.38)	1.34 (1.17-1.53)	<.001	
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	1.05 (0.97-1.13)	1.12 (0.99-1.26)	1.15 (1.01-1.32)	.01	.54
Restricted to myocardial infarction and coronary heart disease death						
Cases/person-years	151/1 018 680	161/1 311 173	38/229 694	35/135 197		
Incidence rate per 100 000 person-years (95% CI)[e]	14.8 (9.5-20.2)	12.4 (7.9-16.9)	16.2 (4.3-28.0)	24.4 (7.2-41.6)		
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	0.83 (0.66-1.04)	0.98 (0.69-1.41)	1.09 (0.75-1.59)	.71	.55
Updated shift work[g]						
Cases/person-years	589/554 846	1077/872 476	328/222 286	233/118 813		
Incidence rate per 100 000 person-years (95% CI)[e]	115.8 (91.2-140.4)	137.4 (116.2-158.6)	161.9 (116.3-207.6)	190.5 (125.1-255.8)		
Age-adjusted model, HR (95% CI)	1 [Reference]	1.18 (1.06-1.30)	1.40 (1.22-1.61)	1.59 (1.36-1.85)	<.001	
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	1.12 (1.01-1.24)	1.19 (1.04-1.37)	1.27 (1.09-1.48)	.001	.84

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study.

[a] A total of 3519 coronary heart disease cases (ie, nonfatal myocardial infarction, coronary heart disease–attributed death, angiogram-confirmed angina pectoris, angioplasty, coronary artery bypass graft surgery, and coronary artery stents) occurred during 24 years of follow-up in the NHS2 (N = 115 535).

[b] Based on category midpoints, except for ≥10 years, for which the midpoint was set to 10 years.

[c] Based on the interaction between shift work category midpoints (except for ≥10 years, for which the midpoint was set to 10 years) and time (in 2-year cycles).

[d] Assessed in 1989.

[e] Incidence rates and 95% CIs are standardized relative to the age distribution of women who reported no history of rotating night shift work, separately for each cohort.

[f] Multivariable-adjusted model including age, physical activity (metabolic equivalent task–hours per week, in quintiles), diet (Alternative Healthy Eating Index score,[12] in quintiles), alcohol consumption (none, 0.1-5, 5.1-10, 10.1-20, or >20 g/d), pack-years of smoking (continuous), parental history of myocardial infarction prior to age 60 years (yes or no), menopausal status (premenopausal vs postmenopausal), parity (nulliparous, 1 child, 2 children, or ≥3 children), hormone therapy (ever, never, or premenopausal), multivitamin use (yes or no), acetaminophen use (yes or no), nonsteroidal anti-inflammatory drug use (yes or no), aspirin use (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), diabetes (yes or no), body mass index (<25, 25-29.9, 30-34.9, or ≥35), race (white, black, or other), and husband's highest educational level (up to high school diploma, college degree, or graduate school level or similar).

[g] Updated shift work refers to cumulative duration of rotating night shift work reported up to 2007.

multivariable HR, 1.19 [95% CI, 1.04-1.37]; incidence rate for ≥10 years, 190.5; multivariable HR, 1.27 [95% CI, 1.09-1.48]; *P*<.001 for trend) (Table 3), compared with women without a history of rotating night shift work (incidence rate, 115.8). In the NHS2, CHD risk also decreased with increasing time since quitting shift work (*P*<.001 for trend) (eTable 2 in the Supplement).

When analyses were restricted to MI and CHD deaths, overall, results were similar in the NHS (Table 2) but were attenuated in the NHS2 (Table 3). Results remained largely unchanged with further adjustment for sleep duration and social support (eTable 3 in the Supplement).

In women without a history of diabetes, hypertension, or elevated cholesterol levels, there was a significant trend of increased CHD risk with longer duration of shift work in the NHS (*P* = .004 for trend) (**Table 4**) but not in the NHS2 (*P* = .11 for trend).

In analyses stratified by BMI, a significant dose-response relationship between shift work and CHD risk across all BMI categories in the NHS was observed (eTable 4 in the Supplement), with highest estimates among obese women (test for interaction, 10.9; *P* = .05). In the NHS2, there was a significant dose-response relationship between shift work and CHD risk only in obese women (*P* = .002 for trend) but not in normal-weight or overweight women (*P*=.53 and *P*=.47 for trend for normal-weight and overweight women, respectively); the interaction between shift work and BMI was not significant (test for interaction, 10.4; *P* = .06).

Discussion

This prospective cohort study examined the association of rotating night shift work with CHD incidence over 24 years of follow-up and found that 5 years or more of rotating night shift work was associated with a significantly increased risk of CHD. The results suggest that recent shift work might be most relevant, as significantly stronger associations were observed in the first vs second part of follow-up in the NHS (27% vs 13% increased risk for ≥10 years of rotating night shift work exposure), in addition to an association between decreasing CHD risk with increasing time since quitting shift work in the NHS2.

Table 4. Shift Work and Risk of Coronary Heart Disease in Women Without Diabetes, Hypertension, or Hypercholesterolemia[a]

Cohort	Baseline History of Rotating Night Shift Work[b] None	<5 y	5-9 y	≥10 y	*P* Value for Trend[c]	*P* Value for Interaction, Shift Work × Time[d]
NHS, 1988-2012						
Cases/person-years	723/319 135	791/316 198	157/47 860	260/75 528		
Incidence rate per 100 000 person-years (95% CI)[e]	301.4 (243.5-359.2)	323.7 (263.0-384.4)	409.4 (238.3-580.5)	380.0 (255.1-504.9)		
Age-adjusted model, HR (95% CI)	1 [Reference]	1.06 (0.96-1.18)	1.37 (1.15-1.63)	1.36 (1.17-1.57)	<.001	
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	1.08 (0.97-1.19)	1.29 (1.08-1.54)	1.17 (1.01-1.36)	.004	.24
NHS2, 1989-2013						
Cases/person-years	720/748 075	1001/966 924	193/165 593	134/92 148		
Incidence rate per 100 000 person-years (95% CI)[e]	100.6 (81.1-120.2)	112.1 (93.6-130.7)	122.9 (74.3-171.5)	136.8 (78.8-194.9)		
Age-adjusted model, HR (95% CI)	1 [Reference]	1.09 (0.99-1.20)	1.17 (1.00 -1.38)	1.28 (1.06-1.54)	.003	
Multivariable-adjusted model, HR (95% CI)[f]	1 [Reference]	1.09 (0.99-1.20)	1.10 (0.94 -1.30)	1.13 (0.94 -1.36)	.11	.78

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study.

[a] All women who reported any of those comorbidities at baseline or throughout follow-up were excluded from those analyses, both in the NHS (N = 43 557) and the NHS2 (N = 98 126).

[b] Assessed in 1988 for the NHS and in 1989 for the NHS2.

[c] Based on category midpoints, except for ≥10 years, for which the midpoint was set to 10 years.

[d] Based on the interaction between shift work category midpoints (except for ≥10 years, for which the midpoint was set to 10 years) and time (in 2-year cycles).

[e] Incidence rates and 95% CIs are standardized to the age distribution of women who reported no history of rotating night shift work, separately for each cohort.

[f] Multivariable-adjusted model including age, physical activity (metabolic equivalent task-hours per week, in quintiles), diet (Alternative Healthy Eating Index score,[12] in quintiles), alcohol consumption (none, 0.1-5, 5.1-10, 10.1-20, or >20 g/d), pack-years of smoking (continuous), parental history of myocardial infarction prior to age 60 years (yes or no), menopausal status (premenopausal vs postmenopausal), parity (nulliparous, 1 child, 2 children, or ≥3 children), hormone therapy (ever, never, or premenopausal), multivitamin use (yes or no), acetaminophen use (yes or no), nonsteroidal anti-inflammatory drug use (yes or no), aspirin use (yes or no), body mass index (<25, 25-29.9, 30-34.9, or ≥35), race (white, black, or other), and husband's highest educational level (up to high school diploma, college degree, or graduate school level or similar).

In this younger cohort, when using cumulatively updated shift work history, a higher CHD risk was observed, with 12%, 19%, and 27% increased risk for less than 5 years, 5 to 9 years, and 10 years or more of shift work, respectively. Results were similar overall when restricting to women without hypertension, diabetes, or hypercholesterolemia, suggesting that these conditions may not be the prime mediators of observed associations between shift work and CHD. In summary, the present analysis indicated that rotating night shift work was associated with increased CHD risk in a duration-dependent manner and that this risk waned over time.

Results were consistent with a recent meta-analysis that found a 24% increased risk of "any coronary event" in shift workers despite significant heterogeneity detected across 28 studies, presumably due to heterogeneous outcome and exposure definitions.[8] The present study was based on a definition of rotating night shift work (≥3 night shifts per month) that has been used extensively in existing literature, although it did not incorporate more precise intensity measures related to frequency and actual working times.[13,14]

Lifetime history of rotating night shift work was queried on average at age 55 years in the NHS, when women are less likely to begin new shift work schedules; in the NHS2, women were asked about shift work history when they were in their mid-30s, with updated shift work assessments throughout follow-up. In the NHS, CHD risk associated with rotating night shift work seemed to wane over time, so that after 20 years of follow-up, the CHD risk associated with 10 years or more of exposure was not significantly elevated. In 1995, Kawachi et al[7] reported that 6 years or more of rotating shift work was associated with 51% increased CHD risk after multivariable adjustment, based on 4 years of follow-up and 292 CHD cases in the NHS. The absolute incidence rate difference corresponded to 86.2 per 100 000 person-years (comparing never shift workers with women with a history of ≥10 years of rotating night shift work) and was of modest magnitude. The rate difference was also comparable with the one reported in the present analysis, when restricting to the primary end points of Kawachi and colleagues (ie, MI and CHD death) and the first 12 years of follow-up in the NHS (crude absolute incidence rate difference, 91.6).

Concomitantly, higher risk estimates for updated shift work were observed in the NHS2, and this CHD risk significantly decreased with increasing time since quitting shift work, lending further support to the suggestion that recent shift work was particularly relevant for CHD risk—a new finding that warrants replication. Overall, the relative CHD risk associated with rotating night shift work was statistically significant. However, the increased CHD risk was found in a small group of women, those who worked 5 or more years on rotating night shifts (only 15% of all women in the study population). Hence, the absolute risk and public health impact of night work—given confirmation of those results—would therefore be small. Nonetheless, because changes in shift work schedules poten-

tially could reduce such risk, it is important to further explore the relationship between shift schedules and CHD risk.

In this study, the CHD outcomes examined reflect trends in CHD care[15,16] and included CABG surgery, angiogram-confirmed angina pectoris, angioplasty, and stents in addition to MI and CHD death. As stated by Hoffmann,[17] an MI represents a relatively late stage of a long, ongoing disease process[18]; to capture earlier manifestations of CHD, the outcome definition also encompassed angiogram-confirmed angina pectoris and angioplasty. The analyses demonstrated a significant dose-response relationship between rotating night shift work exposure and this more comprehensive CHD outcome. In the NHS, results were similar when restricting analyses to MI and CHD death—the end points most other studies have examined. In the NHS2, associations were no longer statistically significant when analyses were restricted to MI and CHD death. There were many fewer cases—only 1 in 10 cases was an MI or CHD death—thus, there was less power to detect a significant association. Age differences between the 2 cohorts (mid-50s in the NHS vs mid-30s in the NHS2 at baseline in 1988 and 1989, respectively) and technological advances resulting in different standards of care[16] may explain these findings. The findings also suggest the importance of evaluating a broader CHD end point in relation to shift work, as part of the association could otherwise be concealed by secondary and tertiary prevention.

Whether shift work was associated with increased CHD risk in the absence of hypertension, hypercholesterolemia, and diabetes was another question of this study. A previous study found no association between CHD-related disability and mortality over 22 years in shift workers vs day workers after excluding individuals with cancer, angina pectoris, nonfatal MI, obstructive pulmonary disease, hypertension, or diabetes mellitus prior to baseline.[19] In this study, when participants with hypertension, elevated cholesterol levels, or diabetes were excluded at baseline and throughout follow-up, a significant dose-response relationship between rotating night shift work and CHD risk was observed in the NHS but not in the NHS2. Overall, this analysis supported the hypothesis that shift work per se—and the associated disruption of biological and social rhythms—could have increased CHD risk, even in the absence of or with only subclinical manifestations of potentially mediating comorbidities such as hypertension, hypercholesterolemia, or diabetes.

Obesity has been associated with a higher risk of CHD,[20,21] such as MI and CHD death.[22] All analyses were therefore adjusted for BMI (updated throughout follow-up), and additional analyses examined whether the effects of shift work varied by BMI. There was suggestive evidence for effect modification by BMI. Although these results warrant replication, women who were overweight might have been at an even higher risk of CHD if they simultaneously worked rotating night shifts. Residual confounding by BMI could be an alternate explanation; however, as analyses were adjusted for BMI continuously in each stratum, this appeared a less likely explanation.

In the past 2 decades, sleep disturbances, psychosocial stress, and social isolation have been identified as important contributors to CHD risk.[23-27] Therefore, additional analyses adjusted for sleep and social support, and results remained largely unchanged. However, given that shift work may affect both sleep and social support,[4] further research in populations with more extensive information on sleep duration, quality, and timing as well as work hours seems warranted. In addition, circadian misalignment—where the biological, endogenous rhythm is asynchronous with behavioral cycles of activity, sleep, and food intake—may be a key mechanism linking shift work to chronic disease,[28,29] including cardiovascular disease.[2,3,30] Future studies might also explore whether an individual's endogenous biological rhythm (also referred to as chronotype)[31] alters the association between lifetime history of rotating night shift and CHD risk, as early chronotypes experience higher levels of circadian misalignment and sleep curtailment during night shifts[32] and might therefore show higher CHD risk related to rotating night shift work.

This study has several strengths of note. It is large, with more than 10 000 incident CHD cases over 24 years of follow-up, and MI and CHD death were confirmed by medical and death records. Detailed information on a wide range of potential confounding factors was available, and most of them were updated regularly throughout follow-up. This study was also based on one of the few cohorts with detailed lifetime shift work exposure information.

Several limitations are also noteworthy. Conclusions can be generalized to women only, and health effects of shift work and pathways may be different in men and women.[33] As in all observational studies, even though known potential confounding factors were controlled for, confounding due to unmeasured differences in behaviors or other factors may still exist. This study relied on self-reports for angiogram confirmed angina pectoris, CABG surgery, angioplasty and stents, but validation studies have demonstrated a high accuracy of self-reports from these participants, all of whom are registered nurses.[34,35] The exposure assessments lacked information on intensity of night shift work and physiological measures that may be affected by shift work. Additionally, as information on permanent night shift work over time was not collected, women with such schedules might have been included in the reference group. If permanent night shift workers had a higher CHD risk compared with never rotating shift workers, this would have biased results toward the null. Future studies should include a more detailed assessment of work hours and job demands, ideally in conjunction with chronotype and sleep timing measures, to enable more detailed studies of circadian strain on coronary health.[14] Furthermore, studying CHD-related biomarkers (eg, triglycerides, cholesterol levels, carotid plaque, or hemoglobin A_{1c})[17,36] might be useful in understanding underlying mechanisms.

Conclusions

Among women who worked as registered nurses, longer duration of rotating night shift work was associated with a statistically significant but small absolute increase in CHD risk. Further research is needed to explore whether the association is related to specific work hours and individual characteristics.

ARTICLE INFORMATION

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