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Association between rotating night shift work and risk of coronary heart disease among women

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Abstract

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

Objective—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 over 24 years in the Nurses' Health Studies (NHS (1988-2012): N=73,623, and NHS2 (1989-2013): N=115,535).

Exposure—Questionnaire-based lifetime history of rotating night shift work (≥3 night shifts/ month, plus day and evening shifts) at baseline; also updated every 2-4yrs in NHS2.

Main Outcomes and Measures—Incident CHD, i.e. non-fatal myocardial infarction, CHD death, angiogram-confirmed angina pectoris, coronary artery bypass grafting (CABG), stents, and angioplasty.

Results—During follow-up, 7,303 incident CHD cases in NHS (mean age at baseline: 54.5yrs) and 3,519 in NHS2 (34.8yrs) occurred. In multivariable adjusted Cox proportional hazards

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models, increasing years of baseline rotating night shift work were associated with a significantly higher CHD risk in both cohorts (NHS: age-standardized incidence rate (IR)$_{<5yrs}$ per 100,000 person-years=435.1, hazard ratio (HR)$_{<5yrs}$=1.02, 95% confidence interval (CI)=0.97-1.08, IR$_{5\text{-}9yrs}$=525.7, HR$_{5\text{-}9yrs}$=1.12, 95%CI=1.02-1.22, IR$_{\geq 10yrs}$=596.9, HR$_{\geq 10yrs}$=1.18, 95%CI=1.10-1.26; P$_{trend}$<0.001; NHS2: IR$_{<5yrs}$=130.6, HR$_{<5yrs}$=1.05, 95%CI=0.97-1.13; IR$_{5\text{-}9yrs}$=151.6, HR$_{5\text{-}9yrs}$=1.12, 95%CI=0.99-1.26; HR$_{\geq 10yrs}$=178.0, HR$_{\geq 10yrs}$=1.15, 95%CI=1.01-1.32; P$_{trend}$=0.01), compared to women who never worked rotating night shifts (NHS: IR$_{never}$=425.5, NHS2: IR$_{never}$=122.6). In NHS, the association between duration of rotating night shift work and CHD was stronger in the first half of follow-up (IR$_{<5yrs}$=382.4, HR$_{<5yrs}$=1.10, 95%CI=1.01-1.21, IR$_{5\text{-}9yrs}$=483.1, HR$_{5\text{-}9yrs}$=1.19, 95%CI=1.03-1.39, IR$_{\geq 10yrs}$=494.4, HR$_{\geq 10yrs}$=1.27, 95%CI =1.13-1.42, P$_{trend}$ <0.001) than in the second half (IR$_{<5yrs}$=424.8, HR$_{<5yrs}$=0.98, 95%CI=0.92-1.05, IR$_{5\text{-}9yrs}$=520.7, HR$_{5\text{-}9yrs}$=1.08, 95%CI=0.96-1.21, IR$_{\geq 10yrs}$=556.2, HR$_{\geq 10yrs}$=1.13, 95%CI =1.04-1.24, P$_{trend}$=0.004, P$_{Interaction}$=0.02), suggestive of waning risk after cessation of shift work. Longer time since quitting shift work was associated with decreased CHD risk among ever shift workers in NHS2 (P$_{trend}$<0.001).

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.

Introduction

Societal and economic demands push towards an increase of 24-hour availability, in health care settings as well as 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. examined the association between rotating night shift work and CHD in the Nurses' Health Study (NHS) over four years of follow-up and reported a 51% significant increase in CHD risk (nonfatal myocardial infarction and CHD death) among women with more than six years of rotating night shift work after multivariate adjustment (incidence rate per 100,000 person-years, 156.1 compared to 75.4 in women who never worked night shifts).[7] 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] This present study re-assessed 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 coronary heart disease (angiogram-confirmed angina pectoris, coronary artery stents, angioplasty and coronary artery bypass grafts (CABG)), in addition to non-fatal myocardial infarction 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 shift work in women without diabetes, hypertension, or hypercholesterolemia – potential comorbid mediators of coronary heart disease.

Methods

Study Population

The NHS and NHS2 are ongoing, prospective cohort studies. The NHS began in 1976 when 121,701 registered US nurses aged 30 to 55 years responded to a baseline questionnaire.[9] The NHS2 started in 1989, including 116,430 registered US nurses aged 25 to 42 years. In both cohorts, biennial follow-up questionnaires have been mailed since then 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 Institutional Review Board (IRB); 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 or more 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 NHS2. In all analyses, night shift work information was carried forward for one questionnaire cycle in 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 myocardial infarction (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 coronary heart disease, including self-reported cases of CABG, 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 four years. Dietary habits were assessed using a semi-quantitative, validated food frequency questionnaire (FFQ),[11] calculating the Alternative Healthy Eating Index (AHEI), which has

previously been found to be a reliable predictor of coronary heart disease in these cohorts.[12] Parity was updated until 1996 and 2009 for NHS and NHS2, respectively, and subsequently carried forward. Husband's educational attainment (a proxy for socio-economic status assessed in 1992 in NHS and in 1999 in NHS2), family history of MI before the age of 60 (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 the women have 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 (HR) and 95% confidence intervals (CI) across rotating night shift work categories (none, <5, 5 to 9, and ≥10 years). Women with no history of rotating night shift work comprised the reference category in all analyses. P-trend calculations 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 (i.e., mid-point of categories) by time in all models, and its significance was evaluated using the Wald statistic. Sensitivity analyses restricted the outcome was restricted to nonfatal MI and CHD death. Additional sensitivity analyses restricted to participants with no baseline history of major comorbidities potentially mediating CHD (i.e., 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 60yrs, diet quality (AHEI,[12] without the alcohol and multivitamin components, in quintiles), physical activity (MET-hours/week; in quintiles), body-mass index (BMI, in kg/m^2: <25, 25-29, 30-35, >35), cumulative pack-years smoked (continuous), alcohol intake (none, 0.1–5, 5.1–10, 10.1–20, >20g/day), parity (nulliparous, 1, 2, ≥3 children), menopausal status (pre- or postmenopausal), postmenopausal hormone use (pre-menopausal, ever, 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/no), acetaminophen use (yes/no), non-steroidal anti-inflammatory drug use (yes/no), aspirin use (yes/no), hypertension (yes/no), diabetes (yes/no), and hypercholesterolemia (yes/no). In additional analyses, models were adjusted for sleep duration (<6, 6-7, 8-9, ≥10 hours/day) and social support (yes/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 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 NHS2, analyses also examined the association between cumulative time since quitting rotating night shift work (never, current, <12, 12-24, >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, and >30kg/m^2) 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 chi-square statistics.

The *a priori* hypothesis was that rotating night shift work increased CHD risk, and all secondary analyses were pre-planned. Analyses were conducted with SAS software, version 9.4. (SAS Institute, Inc., Cary, NC) with a 2-sided significance threshold of $p<0.05$.

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 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 two 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 (7,303 in NHS and 3,519 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 to women in NHS, women in NHS2 were younger, more likely to be nulliparous, had slightly lower alcohol consumption, reported less pack-years of smoking, less comorbid conditions, and took less medication and multi-vitamin supplements. With increasing duration of rotating night shift work, women were heavier in both cohorts. Also, a lower proportion of women had husbands with graduate-level education across categories of shift work, and pack-years of smoking and self-reports of hypertension increased in NHS; in NHS2, a greater proportion of nulliparous women and acetaminophen users were observed with increasing duration of rotating night shift work.

Compared to women without a history of rotating night shift work (IR_{NHS}=425.5 and IR_{NHS2}=122.6), women who worked <5 years of shift work at baseline did not have a significantly increased CHD risk in age-adjusted analyses, (Tables 2 and 3), but there was a significant association between longer durations of shift work and CHD risk (NHS: $HR_{5\text{-}9yrs}$=1.21, 95%CI=1.11-1.33, $IR_{5\text{-}9yrs}$=525.7; $HR_{\geq 10yrs}$=1.36, 95%CI=1.27-1.46, $P_{trend}<0.001$, $IR_{\geq 10yrs}$=596.9; NHS2: $HR_{5\text{-}9yrs}$=1.22, 95%CI=1.08-1.38, $IR_{5\text{-}9yrs}$=151.6; $HR_{\geq 10yrs}$=1.34, 95%CI=1.17-1.53, $IR_{\geq 10yrs}$=178.0, $P_{trend}<0.001$).

Multivariable (MV) adjustment for known CHD risk factors attenuated these estimates, but the elevated risk observed for ≥5yrs of shift work persisted in NHS ($MVHR_{5\text{-}9yrs}$=1.12, 95%CI=1.02-1.22; $MVHR_{\geq 10yrs}$=1.18, 95%CI=1.10-1.26, P_{trend}<0.001), and for ≥10 yrs of shift work in NHS2 ($MVHR_{5\text{-}9yrs}$=1.12, 95%CI=0.99-1.26; $MVHR_{\geq 10yrs}$=1.15, 95%CI=1.01-1.32, P_{trend}=0.01).

In NHS, there was a significant interaction between rotating night shift work exposure and time (by 2-year period, Table 2, $P_{interaction}$<0.001), 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 were observed also with shorter durations of shift work exposure ($MVHR_{<5yrs}$=1.10, 95%CI=1.01-1.21; $IR_{<5yrs}$=382.4; $MVHR_{5\text{-}9yrs}$=1.19, 95%CI=1.03-1.39; $IR_{5\text{-}9yrs}$=483.1, $MVHR_{\geq 10yrs}$=1.27, 95%CI=1.13-1.42, $IR_{\geq 10yrs}$=494.4, P_{trend}<0.001, $P_{interaction}$=0.02 for first *vs.* second half of follow-up). In the second half of follow-up, compared to women who never worked rotating night shifts (IR_{Never}=436.6.0), only those who worked ≥10yrs of shift work had a significantly elevated CHD risk ($MVHR_{\geq 10yrs}$=1.13, 95%CI=1.04-1.24, $IR_{\geq 10yrs}$=556.2, P_{trend}=0.004). The association between shift work and CHD risk was not significant in the last four years of follow-up (2008-2012; $MVHR_{<5yrs}$=0.85, 95%CI=0.70-1.03, $IR_{<5yrs}$=219.9; $MVHR_{5\text{-}9yrs}$=0.88, 95%CI=0.62-1.26; $IR_{5\text{-}9yrs}$=247.2, $MVHR_{\geq 10yrs}$= 1.04, 95%CI=0.80-1.35, $IR_{\geq 10yrs}$=306.3, P_{trend}=0.94, eTable1).

All categories of rotating night shift work showed a significantly elevated CHD risk when shift work history was cumulatively updated in NHS2 ($MVHR_{<5yrs}$=1.12, 95%CI=1.01-1.24, $IR_{<5yrs}$=137.4; $MVHR_{5\text{-}9yrs}$=1.19, 95%CI=1.04-1.37, $IR_{5\text{-}9yrs}$=161.9; $MVHR_{\geq 10yrs}$=1.27, 95%CI=1.09-1.48, $IR_{\geq 10yrs}$=190.5, P_{trend}<0.001, Table 3), as compared to women without a history of rotating night shift work (IR_{Never}=115.8). In NHS2, CHD risk also decreased with increasing time since quitting shift work (P_{trend}<0.001, eTable2).

When analyses were restricted to MI and CHD deaths, overall, results were similar in NHS (Table 2), but attenuated in NHS2 (Table 3). Results remained largely unchanged with further adjustment for sleep duration and social support (eTable3).

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 NHS (P_{trend}=0.004, Table 4), but not NHS2 (P_{trend}=0.11).

In analyses stratified by BMI, a significant dose-response relationship between shift work and CHD risk across all BMI categories in NHS was observed (eTable4), with highest estimates amongst obese women (test for interaction: $\chi^2(5)$ =10.9, p=0.05). In NHS2, there was a significant dose-response relationship between shift work and CHD risk only in obese women (P_{trend}=0.002), but not in normal-weight or overweight women (P_{trend}>0.4); the interaction between shift work and BMI was not significant, ($\chi^2(5)$ =10.4, p=0.06).

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 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 NHS (27% *vs.* 13% increased risk for ≥10yrs of rotating night shift work exposure), in addition to an association between decreasing CHD risk with increasing time since quitting shift work in NHS2. In this younger cohort, when using cumulatively updated shift work history, a higher CHD risk was observed, with a 12%, 19% and 27% increased risk for <5yrs, 5 to 9yrs, and ≥10yrs of shift work, respectively–Results were overall similar 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 23-24% 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/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 in NHS, when women are less likely to begin new shift work schedules; in NHS2, women were asked about shift work history when they were in their mid-thirties, with updated shift work assessments throughout follow-up. In 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 of exposure was not significantly elevated. In 1995, Kawachi et al.[7] reported in NHS that ≥6yrs of rotating night shift work were associated with 51% increased CHD risk after multivariable adjustment, based on 4 years of follow-up and 292 CHD cases. The absolute rate difference corresponded to 86.2/100,000 person-years (comparing never shift workers to women with a history of ≥10yrs of rotating night shift work) and was of modest magnitude. The rate difference was also comparable to the one reported in the present analysis, when restricting to the primary endpoints of Kawachi and colleagues (i.e., MI and CHD death) and the first 12 years of follow-up in NHS (crude absolute incidence rate difference=91.6).

Concomitantly, higher risk estimates for updated shift work were observed in 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 percent 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 and associated light patterns potentially could reduce such risk, it is important to further explore the relation between shift schedules, light at night, and CHD risk.

In this study, the CHD outcomes examined reflect trends in CHD care,[15,16] including CABG, angiogram-confirmed angina pectoris, angioplasty and stents, in addition to myocardial infarction and CHD death. As stated by Hoffmann,[17] a myocardial infarction represents a relatively late stage of a long, ongoing disease process;[18] thus, the definition of CHD was extended by including angina pectoris and angioplasty, aiming to capture earlier manifestations of coronary heart disease. The analyses demonstrated a significant dose-response relationship between rotating night shift work exposure and this more comprehensive CHD outcome. In NHS, results were similar when restricting analyses to MI and CHD death – the endpoints most other studies have examined. In NHS2, associations were no longer statistically significant when analyses were restricted to MI and CHD death. There were much fewer cases - only one in ten cases was an MI or CHD death – and thus less power to detect a significant association. Age differences between the two cohorts (mid-fifties in NHS *vs.* mid-thirties in NHS2 at baseline in 1988 and 1989) and technological advances resulting in different standards of care[16] may explain these findings. They also suggested the importance of evaluating a broader CHD endpoint 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 shift- versus day-workers after excluding individuals with cancer, angina pectoris, non-fatal MI, obstructive pulmonary disease, hypertension, or diabetes mellitus prior to baseline.[19] Here, 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 in NHS, but not NHS2, was observed. 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 coronary heart disease,[20,21] such as myocardial infarction 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. Though these results warrant replication, women who were overweight might have been at an even higher risk for CHD if they simultaneously worked rotating night shifts. Residual confounding by BMI should be considered as an alternate explanation; however, as analyses were adjusted for BMI continuously in each stratum, this appeared a less likely explanation.

In the past two 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 >10,000 incident CHD cases over 24 years of follow-up, and confirmed endpoints of MI and CHD death 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, there might have been still uncontrolled confounding due to unmeasured differences in behaviors or other factors. This study relied on self-reports for angiogram confirmed angina pectoris, CABG, 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 as compared to never rotating shift workers, this would have biased results towards 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 (e.g., triglycerides, cholesterol levels, carotid plaque, or HbA1c)[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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age and age-adjusted characteristics of participating women at baseline by rotating night shift work history

Frequencies are given reported in absolute percent numbers and percentages (%); values are means (standard deviation), unless specified otherwise. [a] IQR = Interquartile range; MI= myocardial infarction.

	Rotating Night Shift Work Exposure (≥ 3 night shifts per month)							
	NHS (1988)				NHS2 (1989)			
Sample Size	**None *30,012***	**<5 yrs *30,122***	**5-9 yrs *4,955***	**≥10 yrs *8,534***	**None *43,657***	**<5 yrs *56,179***	**5-9 yrs *9,866***	**≥10 yrs *5,833***
Age	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)
Race, No. (%, white)	29,390 (98)	29,424 (98)	4,832 (98)	8,250 (97)	42,075 (96)	53,501 (95)	9,337 (95)	5,479 (95)
Parity, No. (%)								
Nulliparous	1,434 (5)	1,795 (6)	351 (7)	539 (6)	12,111 (28)	17,814 (31)	3,440 (36)	1,795 (37)
1 or 2 child(ren)	10,415 (34)	10,650 (35)	1,761 (36)	2,853 (35)	23,249 (53)	28,704 (51)	4,889 (50)	2,926 (48)
≥3 children	17,750 (60)	17,211 (57)	2,743 (55)	4,956 (57)	8,290 (19)	9,653 (18)	1,536 (15)	1,109 (16)
Parental history of MI under 60 yrs, No. (%, yes)	4,893 (16)	5,081 (17)	879 (18)	1,516 (18)	6,105 (14)	8,294 (15)	1,670 (17)	1,011 (16)
Body Mass Index (BMI, kg/m^2)	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)
BMI <25, No. (%)	18,206 (61)	17,910 (59)	2,683 (54)	50	31,400 (72)	39,851 (71)	6,365 (65)	3,420 (62)
BMI 25-29.9, No. (%)	7,926 (27)	8,107 (27)	1,455 (29)	30	7,693 (18)	10,300 (18)	2,068 (21)	1,330 (22)
BMI 30-34.9, No. (%)	2,645 (9)	2,877 (10)	545 (11)	13	2,837 (7)	3,723 (7)	853 (9)	606 (9)
BMI ≥35, No. (%)	1,235 (4)	1,228 (4)	272 (6)	7	1,727 (4)	2,305 (4)	580 (6)	477 (7)
Pack-years of smoking (median, IQR)[b]	18 (7-34)	18 (6-34)	20 (7-35)	24 (10-39)	10 (5-16)	9 (5-16)	10 (5-17)	11 (6-19)
Graduate school diploma of husband, No. (%)	5,841 (19)	6,346 (21)	840 (17)	1,028 (12)	9,351 (21)	13,810 (25)	2,079 (21)	1,090 (18)
Alcohol intake (g/day, median, IQR)[c]	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)
Diet score (AHEI 2010)[d]	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 (Met-h/week, median, IQR)[e]	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)
Multi-vitamin user, No. (%, yes)	18,518 (62)	19,011 (63)	3,148 (64)	5,325 (62)	23,704 (54)	30,053 (54)	5,254 (53)	3,242 (55)
Aspirin user, No. (%, yes)	18,482 (62)	19,105 (63)	3,122 (63)	5,374 (63)	4,747 (11)	6,119 (11)	1,195 (12)	827 (13)
NSAIDs user, No. (%, yes)[f,f]	9,537 (31)	9,680 (32)	1,575 (32)	2,728 (33)	7,775 (18)	10,986 (20)	2,206 (22)	1,409 (22)
Acetaminophen user, No. (%, yes)[g]	11,110 (37)	11,315 (37)	1,849 (38)	3,204 (39)	9,229 (21)	12,370 (22)	2,292 (23)	1,529 (26)
Postmenopausal, No. (%)	20,735 (71)	21,254 (71)	3,674 (72)	6,866 (74)	965 (2)	1,271 (2)	247 (2)	238 (3)

	Rotating Night Shift Work Exposure (≥ 3 night shifts per month)							
	NHS (1988)				NHS2 (1989)			
Sample Size	**None *30,012***	**<5 yrs *30,122***	**5-9 yrs *4,955***	**≥10 yrs *8,534***	**None *43,657***	**<5 yrs *56,179***	**5-9 yrs *9,866***	**≥10 yrs *5,833***
Current post-menopausal hormone use, No. (%)	6,833 (23)	7,059 (24)	1,122 (22)	1,868 (21)	997 (2)	1,263 (2)	246 (2)	236 (3)
Self-reported hypertension, No. (%)	7,464 (25)	7,641 (26)	1,448 (29)	2,781 (30)	2,270 (5)	2,938 (5)	627 (6)	460 (7)
Self-reported diabetes, No. (%)	1,048 (4)	995 (3)	221 (4)	507 (6)	396 (1)	402 (1)	74 (1)	68 (1)
Self-reported hypercholesterolemia, No. (%)	6,683 (23)	6,837 (23)	1,171 (23)	2,781 (24)	4,493 (10)	5,809 (10)	1,100 (11)	722 (11)
Usual sleep duration[h], No. (%)								
≤6	6,978 (23)	7,506 (25)	1,427 (29)	2,901 (34)	8,939 (20)	12,230 (22)	2,542 (26)	1,670 (28)
7	11,299 (38)	11,353 (38)	1,770 (36)	2,609 (31)	13,835 (32)	17,397 (31)	2,779 (28)	1,552 (26)
8-9	7,661 (26)	7,358 (24)	1,044 (21)	1,709 (19)	9,593 (22)	11,178 (20)	1,680 (17)	892 (16)
≥10	157 (1)	132 (0)	24 (0)	56 (1)	245 (1)	322 (1)	52 (1)	37 (1)
Social support, No. (%, yes)[i]	22,288 (94)	22,667 (94)	3,617 (93)	6,019 (94)	31,370 (94)	39,389 (95)	6,822 (95)	3,930 (94)

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

[b] Cumulative, amongst smokers.

[c] Assessed in 1986 for NHS and in 1991 for NHS2.

[d] Assessed in 1986 for NHS and in 1991 for NHS2. Higher scores as computed by the Alternative Healthy Eating Index (AHEI 2010, Chiuve et al., 2012) reflect a healthier diet.

[e] Weekly energy expenditure in metabolic equivalent hours from recreational and leisure time activities.

[f] Non-steroidal anti-inflammatory drugs (e.g. ibuprofen).

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

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

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

Table 2

Shift Work and Risk of Coronary Heart Disease (CHD) in the NHS

A total of 7,303 CHD cases (i.e. nonfatal myocardial infarction, CHD-attributed death, angiogram-confirmed angina pectoris, angioplasty, coronary artery bypass graft surgery, and coronary artery stents) occurred during 24 years of follow-up in NHS (n=73,623). Results represent hazard ratios (HR) with 95% confidence intervals (95%CI).

Baseline history of rotating night shift work[a]	**None**	**<5 years**	**5 to 9 years**	**≥ 10 years**	***p for trend***[b]	***p for interaction shift work * time***[c]
NHS – 1988 to 2012						
cases/person-years	2,739/643,774	2,857/644,857	568/103,574	1,139/173,571		
Incidence Rate[d] per 100,000 person/years (95%)	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)	1.00 (Ref)	1.02 (0.96-1.07)	1.21 (1.11-1.33)	1.36 (1.27-1.46)	<0.001	
Multivariable-adjusted Model[e] (HR, 95%CI)	1.00 (Ref)	1.02 (0.97-1.08)	1.12 (1.02-1.22)	1.18 (1.10-1.26)	<0.001	<0.001
First vs. second half of follow-up						
NHS – 06/1988- 05/2000						0.02
cases/person-years	915/351,568	1,021/352,490	213/57,612	455/97,899		
Incidence Rate[d] per 100,000 person/years (95%)	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[e] (HR, 95%CI)	1.00 (Ref)	1.10 (1.01-1.21)	1.19 (1.03-1.39)	1.27 (1.13-1.42)	<0.001	0.03
NHS – 06/2000-05/2012						
cases/person-years	1,824/305,036	1,836/305,297	355/48,238	684/79,819		
Incidence Rate[d] per 100,000 person/years (95% CI)	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[e] (HR, 95%CI)	1.00 (Ref)	0.98 (0.92-1.05)	1.08 (0.96-1.21)	1.13 (1.04-1.24)	0.004	0.08
Restricted to MI and CHD death						
NHS – 06/1988-05/2000						
cases/person-years	443/353,659	491/354,846	117/58,026	226/99,022		
Incidence Rate[d] per 100,000 person/years (95%)	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[e] (HR, 95%CI)	1.00 (Ref)	1.12 (0.99-1.28)	1.35 (1.10-1.66)	1.29 (1.09-1.51)	0.001	0.19
NHS – 06/2000-05/2012						
cases/person-years	444/316,989	428/318,083	65/50,714	176/84,689		
Incidence Rate[d] per 100,000 person/years (95%)	106.6 (73.1-140.0)	92.3 (69.1-115.5)	101.5 (36.4-166.5)	133.3 (76.4-190.1)		

Baseline history of rotating night shift work[a]	None	<5 years	5 to 9 years	≥ 10 years	*p for trend*[b]	*p for interaction shift work * time*[c]
Multivariable-adjusted Model[e] (HR, 95%CI)	1.00 (Ref)	0.95 (0.83-1.09)	0.77 (0.60-1.00)	1.09 (0.91-1.30)	0.84	0.56

[a] Assessed in 1988.

[b] Based on category mid-points, except for 10+ years, where the mid-point was set to 10 years.

[c] Based on the interaction between shift work category mid-points (except for 10+ years, where the mid-point was set to 10 years) and time (in 2-year cycles).

[d] Incidence rates and confidence intervals are adjusted to the age distribution of women who reported no history of rotating night shift work, separately for each cohort.

[e] Multivariable-adjusted model including age, physical activity (METs/h per week, in quintiles), diet (Alternative Healthy Eating Index [AHEI] score, Chiuve et al., 2012, in quintiles), alcohol consumption (none, 0.1-5, 5.1-10, 10.1-20, >20g/day) and pack-years of smoking (continuous), parental history of MI <60yrs (yes/no), menopausal status (pre/post), parity (nulliparous, 1 child, 2 children, ≥3 children), post-menopausal hormone use (ever, never, pre-menopausal), multivitamin use (yes/no), acetaminophen use (yes/no), NSAIDs use (yes/no) and aspirin use (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), diabetes (yes/no), body mass index (< 25, 25-29.9, 30-34.9, ≥35), race (white, black, other), and husbands' highest educational level (up to high school diploma, college degree, graduate school level or similar).

Table 3

Shift Work and Risk of Coronary Heart Disease (CHD) in the NHS2

A total of 3,519 CHD cases (i.e. nonfatal myocardial infarction, CHD-attributed death, angiogram-confirmed angina pectoris, angioplasty, coronary artery bypass graft surgery, and coronary artery stents) occurred during 24 years of follow-up in NHS2 (n=115,535). Results represent hazard ratios (HR) with 95% confidence intervals (95%CI).

	None	<5 years	5 to 9 years	≥ 10 years	*p for trend*[a]	*p for interaction shift work * time*[b]
NHS2 – Baseline history of rotating night shift work[c]						
cases/person-years	1,236 /1,007,860	1,673/1,296,585	347/226,580	263/132,971		
Incidence Rate[d] per 100,000 person/years (95%)	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)	1.00 (Ref)	1.06 (0.99-1.14)	1.22 (1.08-1.38)	1.34 (1.17-1.53)	<0.001	
Multivariable-adjusted Model[e] (HR, 95%CI)	1.00 (Ref)	1.05 (0.97-1.13)	1.12 (0.99 -1.26)	1.15 (1.01-1.32)	0.01	0.54
Restricted to MI and CHD death						
cases/person-years	151 /1,018,680	161/1,311,173	38/229,694	35/135,197		
Incidence Rate[d] per 100,000 person/years (95%)	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[e] (HR, 95%CI)	1.00 (Ref)	0.83 (0.66-1.04)	0.98 (0.69-1.41)	1.09 (0.75-1.59)	0.71	0.55
NHS2 – Updated shift work[f]						
cases/person-years	589/554,846	1,077/872,476	328/222,286	233/118,813		
Incidence Rate[d] per 100,000 person/years (95%CI)	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)	1.00 (Ref)	1.18 (1.06-1.30)	1.40 (1.22-1.61)	1.59 (1.36-1.85)	<0.001	
Multivariable-adjusted Model[e] (HR, 95%CI)	1.00 (Ref)	1.12 (1.01-1.24)	1.19 (1.04-1.37)	1.27 (1.09-1.48)	0.001	0.84

[a] Based on category mid-points, except for 10+ years, where the mid-point was set to 10 years.

[b] Based on the interaction between shift work category mid-points (except for 10+ years, where the mid-point was set to 10 years) and time (in 2-year cycles).

[c] Assessed in 1989.

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

[e] Multivariable-adjusted model including age, physical activity (METs/h per week, in quintiles), diet (Alternative Healthy Eating Index [AHEI] score, Chiuve et al., 2012, in quintiles), alcohol consumption (none, 0.1-5, 5.1-10, 10.1-20, >20g/day) and pack-years of smoking (continuous), parental history of MI <60yrs (yes/no), menopausal status (pre/post), parity (nulliparous, 1 child, 2 children, ≥3 children), post-menopausal hormone use (ever, never, pre-menopausal), multivitamin use (yes/no), acetaminophen use (yes/no), NSAIDs use (yes/no) and aspirin use (yes/no), hypertension (yes/no),

hypercholesterolemia (yes/no), diabetes (yes/no), body mass index (< 25, 25-29.9, 30-34.9, ≥35), race (white, black, other), and husbands' highest educational level (up to high school diploma, college degree, graduate school level or similar).

[f] Updated shift work refers to cumulative duration of rotating night shift work women reported until 2007.

Table 4

Shift Work and CHD in women without diabetes, hypertension and hypercholesterolemia

All women who reported any of those comorbidities at baseline, or throughout follow-up, were excluded from those analyses, both in NHS (n= 43,557) and NHS2 (n=98,126). Results represent hazard ratios (HR) with 95% confidence intervals (95%CI). MI=myocardial infarction.

Cohort	**Baseline history of rotating night shift work**[a]				***p for trend***[b]	***p for interaction shift work* time***[c]
NHS – 1988-2012	None	<5 years	5 to 9 years	≥ 10 years		
cases/person-years	723/319,135	791/316,198	157/47,860	260/75,528		
Incidence Rate[d] per 100,000 person/years (95%CI)	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)	1.00 (Ref)	1.06 (0.96-1.18)	1.37 (1.15-1.63)	1.36 (1.17-1.57)	<0.001	
Multivariable-adjusted Model[e] (HR, 95%CI)	1.00 (Ref)	1.08 (0.97-1.19)	1.29 (1.08-1.54)	1.17 (1.01-1.36)	0.004	0.24
NHS2 – 1989-2013						
cases/person-years	720/748,075	1,001/966,924	193/165,593	134/92,148		
Incidence Rate[d] per 100,000 person/years (95%CI)	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)	1.00 (Ref)	1.09 (0.99-1.20)	1.17 (1.00 -1.38)	1.28 (1.06-1.54)	0.003	
Multivariable-adjusted Model[e] (HR, 95%CI)	1.00 (Ref)	1.09 (0.99-1.20)	1.10 (0.94 -1.30)	1.13 (0.94 -1.36)	0.11	0.78

[a] Assessed in 1988 for NHS and in 1989 for NHS2.

[b] Based on category mid-points, except for 10+ years, where the mid-point was set to 10 years.

[c] Based on the interaction between shift work category mid-points (except for 10+ years, where the mid-point was set to 10 years) and time (in 2-year cycles).

[d] Incidence rates and confidence intervals are standardized to the age distribution of women who reported no history of rotating night shift work, separately for each cohort.

[e] Multivariable-adjusted model including age, physical activity (METs/h per week, in quintiles), diet (Alternative Healthy Eating Index [AHEI] score, Chiuve et al., 2012, in quintiles), alcohol consumption (none, 0.1-5, 5.1-10, 10.1-20, >20g/day) and pack-years of smoking (continuous), parental history of MI <60yrs (yes/no), parity (nulliparous, 1 child, 2 children or ≥3 children), menopausal status (pre/post), post-menopausal hormone use (ever, never, pre-menopausal), multivitamin use (yes/no), acetaminophen use (yes/no), NSAIDs use (yes/no) and aspirin use (yes/no), race (white, black, or other), husbands' highest educational level (up to high school diploma, college degree, or graduate school level or similar) and body mass index (< 25, 25-29.9, 30-34.9, ≥35).