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Night shift work and cardiovascular disease biomarkers in female nurses

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Abstract

Background: Night shift work is associated with cardiovascular disease, but its associations with cardiovascular disease biomarkers are unclear. We investigated these associations in a study of female nurses.

Methods: We used data from Nurses' Health Study II for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, C-reactive protein (CRP), and fibrinogen. Sample sizes for our analysis ranged from 458 (fibrinogen) to 3,574 (total cholesterol). From questionnaires, we determined number of night shifts worked in the two weeks before blood collection and total years of rotating night shift work. We used quantile regression to estimate differences in biomarker levels by shift work history, adjusting for potential confounders.

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Results: Nurses working 1-4 recent night shifts had median HDL cholesterol levels 4.4 mg/dL (95% confidence interval [CI]: 0.3, 7.5) lower than nurses without recent night shifts. However, working ≥5 recent night shifts and years of rotating night shift work were not associated with HDL cholesterol. There was no association between recent night shifts and CRP, but median CRP levels were 0.1 (95% CI: 0.0, 0.2), 0.2 (95% CI: 0.1, 0.4), and 0.2 (95% CI: −0.0, 0.4) mg/L higher among nurses working rotating night shifts for 1-5, 6-9 and ≥10 years compared to nurses never working rotating night shifts. These associations were attenuated when excluding postmenopausal women and women taking statins. We observed no associations between night shift work and other biomarkers.

Conclusions: We found suggestive evidence of adverse short-term and long-term effects of night shift work on select cardiovascular disease biomarkers.

Keywords

biomarkers; C-reactive protein; lipids; night shift work; nurses; women

INTRODUCTION

Associations between night shift work and increased risk of CVD have been observed in epidemiologic studies for decades; a recent meta-analysis estimated that every 5 years of night shift work increases the risk of CVD by 7%.[1–3] Night shift work is an integral part of many industries and occupations. In many countries, 15-25% of workers work night shifts, making night shift work a potentially important contributor to the global burden of CVD.[4]

The misalignment of usual day-night routines and sleep restriction experienced by night shift workers may have adverse cardiometabolic effects.[5] For example, a 12-hour shift in usual sleep and wake times resulted in higher plasma glucose and insulin levels, lower leptin levels, and higher systolic blood pressure in one study.[6] Interventional studies show that sleep restriction may have adverse metabolic and hemodynamic effects. In a small trial, individuals allocated 4 hours per night in bed for 10 nights had a significant increase in C-reactive protein (CRP) levels, a finding not observed among those allowed 8 hours per night in bed.[7] These findings were later confirmed in another similar trial and in studies of night workers.[8–10] Other studies show that sleep restriction results in glucose intolerance, elevations in blood pressure, higher levels of inflammatory cytokines, and coronary artery calcification.[11–14]

Despite fairly consistent evidence for associations between night shift work and CVD, and sleep disruption and CVD biomarkers, the results of epidemiologic studies of night shift work and CVD biomarkers have been mixed. Some studies have found associations between shift work and higher levels of plasma lipids and inflammatory markers, including HDL cholesterol, triglycerides, and CRP, but others have not.[15] Proposed reasons for these differences have included varying definitions of “shift work”, differences in the magnitude of the associations between men and women, and differences in the length of time participants have worked night shifts.[15]

The purpose of this study was to investigate associations between night shift work and six CVD biomarkers in a large, prospective study of female nurses, to determine if shift work affects levels of biomarkers that are precursors to CVD. We included the following CVD biomarkers: high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, CRP, and fibrinogen.

MATERIALS AND METHODS

We used data from the Nurses' Health Study II (NHSII). NHSII is an ongoing longitudinal study of 116,429 female registered nurses aged 25-42 years at the 1989 baseline. Nurses completed mailed questionnaires every two years and reported on their lifestyle, health conditions, and health-related behaviors.

Between 1996 and 2001, 29,611 nurses aged 32-54 years provided blood samples for a biomarker substudy. At blood collection, nurses completed a short questionnaire that included information on sociodemographic and lifestyle factors. Blood samples were collected in tubes containing sodium heparin, stored in Styrofoam containers, and shipped on ice to the NHSII laboratory; 95% arrived within 24 hours of collection. At the laboratory, samples were processed and stored in the vapor phase of liquid nitrogen.

All women provided written informed consent for participation. This study was approved by the institutional review board of Brigham and Women's Hospital.

Participant selection

We combined data from 14 previous NHSII biomarker analyses in which one or more of the biomarkers of interest had been assayed: HDL cholesterol (4 studies), LDL cholesterol (4 studies), total cholesterol (7 studies), triglycerides (6 studies), CRP (11 studies), and fibrinogen (1 study). These included 12 nested case-control studies of breast cancer, ovarian cancer, hypertension, ischemic stroke, myocardial infarction, diabetes, Barrett's esophagus, inflammatory bowel disease, early age at menopause, endometriosis, rheumatoid arthritis, and post-traumatic stress disorder, and two cross-sectional studies of alcohol consumption and diet. When participants were included in more than one study for the same biomarker, we randomly included one of their samples in the analysis. Only the controls were included from each case-control study; all participants from the cross-sectional studies were included.

In addition to the inclusion and exclusion criteria for each of the 14 studies, we excluded women with a history of cancer (except non-melanoma skin cancer) at time of blood collection, a history of myocardial infarction or stroke at time of blood collection, and missing values for variables of interest.

Biomarkers

Biomarker concentrations were measured using standard, validated methods. Lipids were measured directly using enzymatic methods; CRP was measured using highly sensitive immunoturbidimetric assays; and fibrinogen was measured using an immunoturbidimetric assay. In the 43 individual assays performed for the 14 studies, the coefficients of variation ranged from 0.3 to 14.1 with the exception of one value of 51.0 (CRP); further investigation

did not find a reason for this high value. Because biomarkers were assayed at different times, we used a correction algorithm to take into account between-batch variability.[16]

For CRP analyses, we excluded participants with values ≥10 mg/L, which could indicate acute infection.[17] Values below the limit of detection (LOD) for CRP were set to LOD/√2. Following visual inspection of biomarker distributions, we excluded two apparent outliers: one in the total cholesterol analysis (499 mg/dL) and one in the triglycerides analysis (2,112 mg/dL).

Exposures

We used two measures of night shift work:

Recent night shift work.—At time of blood collection, nurses reported how many night shifts they worked in the past two weeks (0, 1-2, 3-4, 5-6, ≥6). We grouped these into three categories: 0, 1-4, and ≥5 shifts. These could have been permanent or rotating night shifts.

Duration of rotating night shift work.—On the baseline questionnaire in 1989, nurses reported how many years of rotating night shifts (at least three night shifts per month in addition to days or evenings) they worked in their careers (0, 1-2, 3-5, 6-9, 10-14, 15-19, ≥20). This number was updated based on questionnaires in 1991, 1993, and 1997 which asked the number of months of rotating night shifts worked in the previous two years (0, 1-4, 5-9, 10-14, 15-19, ≥20). When there was a missing value for months of shift work (including in 1995 and 1999, when the question was not asked), we carried forward the response from the prior questionnaire once. We calculated the total years of rotating shifts worked through the time of blood collection by summing the years of rotating night shifts worked before 1989 with the months of rotating shift work reported on subsequent questionnaires. The midpoint of each category was used in the calculation, except for the highest categories, in which the category minimum was used. We categorized rotating shift work into 0, 1-5, 6-9, and ≥10 years for analysis.

Statistical analysis

We performed quantile regression to estimate differences in biomarker levels and 95% confidence intervals (CI) by recent and rotating shift work history. Quantile regression is an alternative to linear regression that models percentiles of the outcome, such as the median (50^{th} percentile), as opposed to the mean.[18] Quantile regression is useful when the outcome is not normally distributed or if there are potentially influential outliers that could affect the mean more than the median, both of which were true for our data. Results from quantile regression are interpreted in the same way as linear regression. For example, quantile regression at the 50^{th} percentile produces the difference in the median value of the outcome between exposed and unexposed participants.

Another use of quantile regression is to conduct regressions at different percentiles of the outcome distribution and to graph the results to show patterns.[18] For example, we could see if night shifts are stronger risk factors for elevated cholesterol levels among nurses who have high cholesterol levels compared to women with low cholesterol levels. We conducted

quantile regressions at the 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentiles of each biomarker outcome distribution and graphed the results. We could not run models for the 10^{th} and 90^{th} percentiles for fibrinogen due to small sample size.

We adjusted all models for age (continuous) and included age^2 terms in the total cholesterol, triglycerides, and CRP models based on model fit. Race/ethnicity (non-Hispanic white, other) was included only in the total cholesterol, triglycerides, and CRP models; there was too little variability in race/ethnicity for it to be included for the other biomarkers. We adjusted the models for body mass index (BMI), smoking, alcohol consumption, and physical activity. Because BMI, smoking, alcohol consumption, and physical activity might be on the causal pathway between exposure (night shift work) and outcome (biomarker level), we used versions of these variables representing measurements that occurred prior to exposure. Using versions measured prior to exposure ensures that the variables are not on the causal pathway and can be adjusted for as confounders in the analysis without inducing bias.[19] For the recent night shift analyses, we used values of BMI, smoking, alcohol consumption, and physical activity that were collected on the biennial questionnaire preceding blood collection. For the analysis of duration of rotating night shift work, we used BMI at age 18 and smoking, alcohol consumption, and physical activity during ages 18-22 years (likely before most participants began working as nurses). Nurses reported information about their behaviors at ages 18-22 years on biennial questionnaires which asked them to recall various aspects of their lifestyle in early adulthood.

The sample size for fibrinogen was too small for the full multivariable models to converge. We therefore only adjusted for age in these models. For all models, we performed a complete-case analysis and excluded observations with missing values for any covariate.

Sensitivity analyses

We did three sensitivity analyses. In the first, we excluded women using statins. Statin use and duration of use were collected on the 1999 questionnaire (up to 3 years after blood collection for some women). We categorized women as statin users if their reported duration of use could have overlapped the date of blood collection. In the second, we excluded women who were postmenopausal at time of blood collection, because CVD biomarker values might change after menopause. In the third, we stratified by BMI at time of blood draw (<25 and ≥ 25 kg/m^2) to investigate differences in the association between nurses at lower and higher risk of CVD.

RESULTS

Characteristics of study participants at time of blood collection are shown in Table I, stratified by recent (two weeks before blood collection) shift work and lifetime history of rotating night shift work. Nurses who worked at least one recent night shift (n = 567) were more likely to be younger, obese, current smokers, and to have consumed less alcohol in the past month than nurses with no recent night shift work (n = 4,760). These differences were less apparent between nurses with (n = 3,493) and without (n = 1,670) a lifetime history of rotating night shifts; most nurses (68%) worked rotating night shifts in their careers. The

distributions of race/ethnicity and physical activity were similar between nurses working and not working night shifts.

The biomarker distributions in the study population are shown in the Supplementary Materials, with clinically established biomarker thresholds for high CVD risk included for comparison. About half of nurses were at low or average risk for CVD based on total cholesterol levels, and over 75% at low or average risk based on triglycerides and CRP levels.

Adjusted median HDL cholesterol levels were lower in nurses working 1-4 night shifts (−4.4, 95% CI: −7.5, −0.3 mg/dL) but not ≥5 night shifts (0.8, 95% CI: −5.0, 2.6 mg/dL) in the two weeks before blood collection compared to nurses with no recent night shifts (Table II). No other biomarkers were associated with recent night shift work.

Years of rotating night shift work was associated with CRP levels, but not with levels of other biomarkers. Nurses with 1-5, 6-9, and ≥10 years of rotating shift work during their career had median CRP levels 0.1 (95% CI: 0.0, 0.2), 0.2 (95% CI: 0.1, 0.4), and 0.2 (95% CI: −0.0, 0.4) mg/L higher than nurses who had never worked rotating night shifts (Table III).

When examining how the associations changed across the biomarker distributions, we found that nurses working 1-4 recent night shifts had lower HDL cholesterol levels than nurses who did not work night shifts fairly uniformly over the HDL cholesterol distribution, although the differences were not statistically significant above the 50^{th} percentile (Figure 1). The association between years of rotating night shifts and CRP was strongest among nurses with the highest CRP levels (Figure 1). For all other biomarkers, which had shown no associations at the median of the distribution, we also found no patterns across the biomarker distributions (Supplementary Materials).

In sensitivity analyses for the HDL cholesterol results, when we excluded nurses using statins and postmenopausal nurses, associations between recent night shift work and HDL cholesterol did not appreciably change (Figure 2). When stratifying by BMI, the association for 1-4 versus 0 recent nights was significant among women with BMI <25 kg/m^2 (−7.8, 95% CI: −11.8, −3.8 mg/dL); in contrast, no association was observed in nurses with BMI ≥25 kg/m^2.

For CRP levels, years of rotating night shifts was no longer associated with CRP levels after excluding women taking statins, or excluding postmenopausal women. Stratified analyses by BMI showed that longer lifetime night shift work duration remained associated with elevated CRP levels among women with BMI ≥25 kg/m^2, but not nurses with lower BMI, although the association was no longer statistically significant (Figure 2).

DISCUSSION

In this large study of female nurses, those working 1-4 night shifts in the past two weeks had lower HDL cholesterol levels than nurses who did not work recent night shifts. Nurses with a history of rotating night shift work had higher CRP levels than those who never worked

rotating night shifts, but associations were attenuated in sensitivity analyses. We did not observe associations between night shift work and other biomarkers.

Although the literature on night shift work and CVD has mixed results overall, associations between night shift work and CVD incidence and mortality consistently show an increased risk of CVD among night shift workers; this risk increases with duration of night shift work.[2] These same associations and trends have been observed in the NHSII population, with nurses working ≥10 years of rotating shift work at the greatest risk for coronary heart disease.[1] The two biomarkers we found associated with night shift work, HDL cholesterol and CRP, are not considered causally related to development of CVD, unlike other biomarkers such as LDL cholesterol and triglycerides, for which we found no associations.[20] Our results therefore suggest that the effect of night shift work on CVD risk might not operate through modifying causal CVD biomarkers.

Associations between night shift work and lipid levels have been inconsistently reported, with some studies finding that night shift work is associated with decreased HDL cholesterol levels and higher triglyceride levels and others finding no association.[15,21] Many studies have found no association between night work and LDL cholesterol, and associations with total cholesterol have been mixed.[15,21] We found a suggestive association between recent night shifts (but not history of rotating night shifts) with HDL cholesterol and no pattern indicating consistent associations between any type of night shift work and LDL cholesterol, total cholesterol, or triglycerides. Although we did not find a dose-response pattern for HDL cholesterol, it is possible that the 1-4 recent night and ≥5 recent night categories are measuring different types of shift work. Because both rotating and permanent night shifts were included in the recent night shift category, women working ≥5 recent night shifts might be more likely to be permanent shift workers and women working 1-4 recent night shifts more likely to be rotating shift workers.

There have been few studies of night shift work and fibrinogen levels; two previous studies found no association.[22,23] In the present study, the small sample size for fibrinogen (n = 458) limited our ability to draw firm conclusions due to wide confidence intervals and inability to control for potential confounders.

There is experimental and epidemiologic evidence that night shift work is associated with elevated CRP levels. In human experiments, CRP levels increased among volunteers subjected to circadian misalignment through a 12 hour delay in normal sleep hours.[5,9] In the present analysis, we found no association between recent night shift work and CRP levels. Other epidemiologic studies have observed higher CRP levels among rotating night shift workers and other night shift workers, consistent with our findings of associations between years of rotating night shifts and CRP levels.[10,22,24] A new finding from our study was a stronger association between night shift work and CRP among nurses who had the highest CRP levels. This could indicate that night shift work is a more important predictor of CRP levels among workers already at higher risk for CVD. Our sensitivity analysis stratified by BMI supports this; we only found the association among nurses who were overweight or obese.

In sensitivity analyses, we excluded nurses who took statins around the time of blood collection and excluded postmenopausal women because statins, menopause, and hormone replacement therapy can affect CVD risk and levels of CVD biomarkers.[25,26] We did not observe associations between night shift work and CRP in these sensitivity analyses. This could be because these populations represented women at lower risk for CVD—some of our other results suggest that the association was strongest among those with characteristics indicative of higher CVD risk. During our study period (1996-2001) statin use was less common than today. Women who took statins were likely at high risk for CVD or had good healthcare access and insurance. By excluding women taking statins, we might have preferentially excluded women with these characteristics from the study, although selection bias might not have occurred if the exclusion was unrelated to exposure (night shift work).

Studies of shift work and CVD biomarkers are difficult to compare because of differences in shift work definitions between studies.[19] This was also a limitation of our study. We did not know if recent night shifts were permanent versus rotating night shifts. For rotating night shifts, we did not know the number and sequence of nights per month, rotational direction, shift length, or other characteristics that could impact severity of circadian disruption.[19] Because the study included nurses from across the country and nurses working in a variety of nursing positions, we would expect a wide variety of shift lengths and patterns. It would be helpful to have more detailed information on shift work in future studies to better understand the potential for circadian disruption to affect CVD biomarker levels. Previous studies have found that clockwise rotation, fewer consecutive night shifts, and other scheduling characteristics are associated with more favorable lipid profiles than other rotating night shift schedules.[19,27,28] Although our analysis of rotating night shifts had the advantage of exclusively investigating a shift type associated with the greatest circadian misalignment, in our analysis of recent night shift work we were unable to exclude nurses working permanent nights to separate the effects of each on CVD biomarker levels.

The large sample sizes for some of our biomarker analyses were strengths of the study. Instead of dichotomizing shift work as ever/never, we were able to investigate three and four categories of shift work to look for dose-response patterns. However, despite the large sample size, our population was not racially or ethnically diverse and we cannot determine if our results are generalizable to women who are not non-Hispanic white.

Our use of quantile regression was also a strength. We modeled the median of the biomarker distributions instead of the mean, reducing the influence of potential outliers or skewed biomarker distributions. By conducting regressions at multiple percentiles of the biomarker distributions, we found that the association between rotating night shift work and CRP was not constant. Because of this variation, if we repeated this analysis in a population with higher CRP levels overall, we might expect to find stronger associations at lower percentiles of the distribution than in our population. This could make it challenging to compare results across studies.

In conclusion, this large study of nurses found associations between recent night shift work and lower HDL cholesterol levels and length of rotating night shift work and higher

CRP levels. Our results add to elucidating the relation between the circadian program, its molecular mediators, and CVD risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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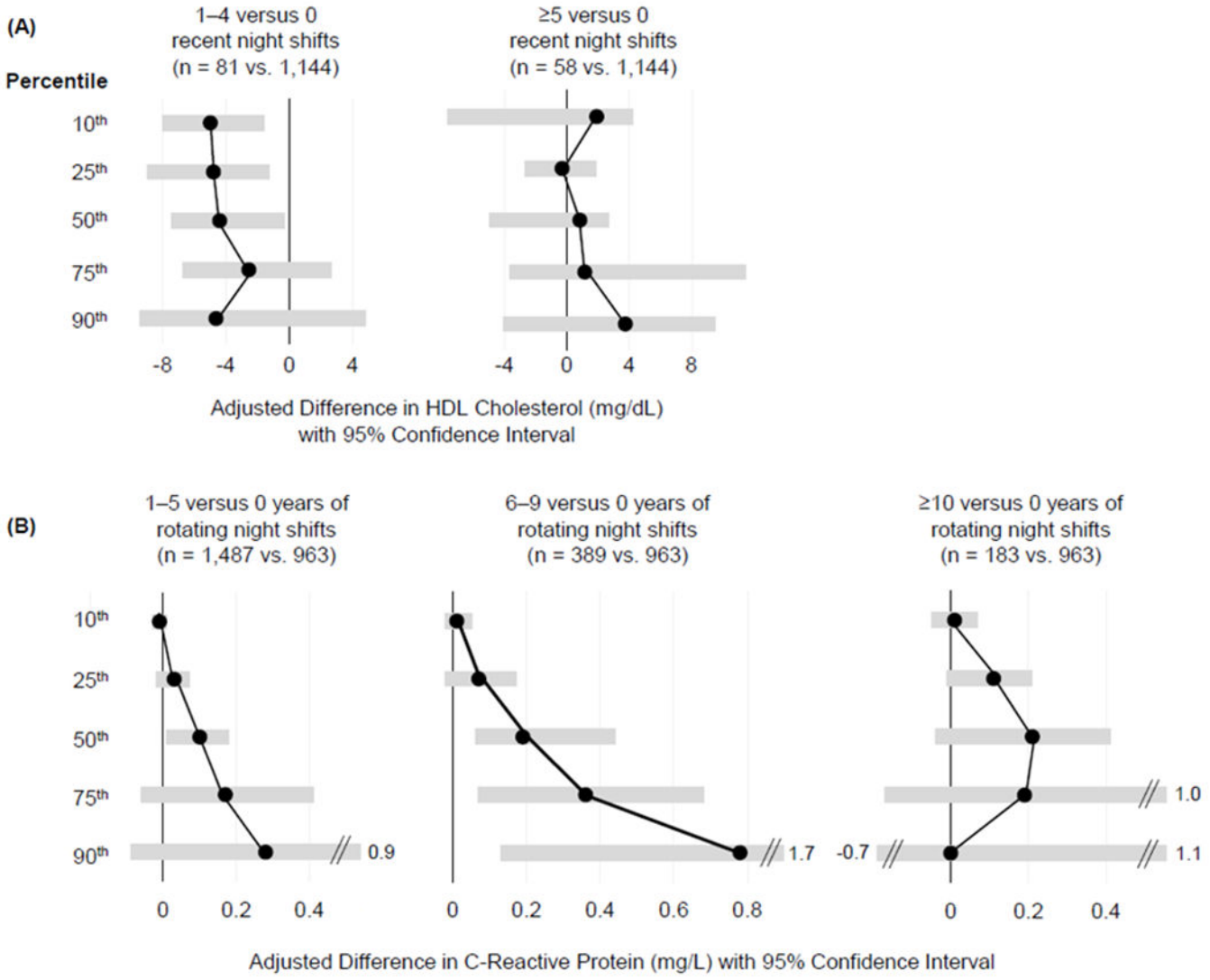

Figure 1.

Adjusted differences in HDL cholesterol and C-reactive protein (CRP) levels between nurses working and not working night shifts. (A) Nurses who worked 1-4 recent night shifts had lower HDL cholesterol levels than those not working recent night shifts at every percentile of the HDL cholesterol distribution. No clear difference was observed for nurses working ≥5 versus 0 recent night shifts. (B) Nurses working 1-5 or 6-9 years of rotating night shift work had higher CRP levels than nurses never working rotating shifts, at all but the lowest percentiles of the CRP distribution. The same pattern was not observed for nurses working ≥10 years of rotating shift work.

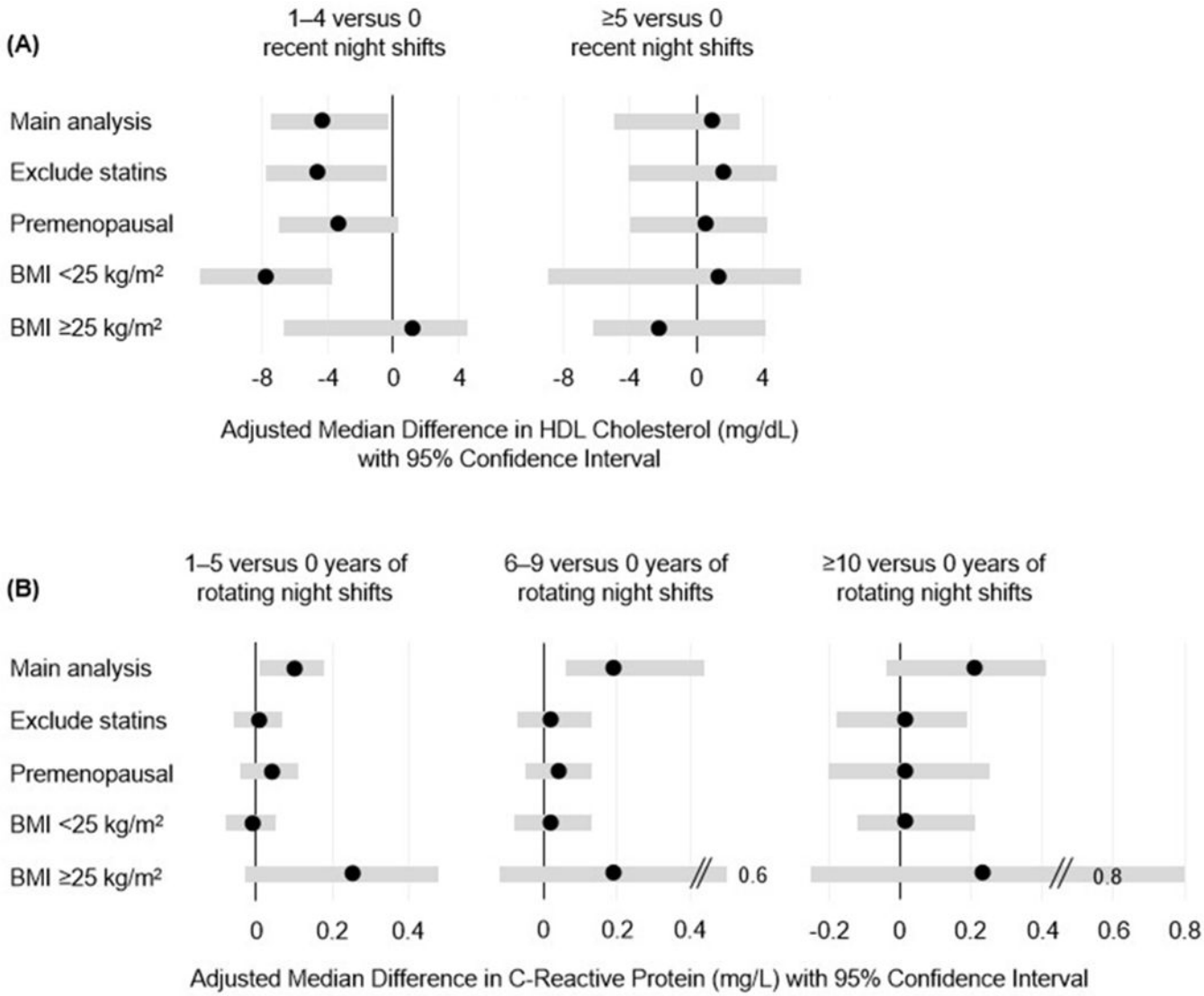

Figure 2.

Sensitivity analyses. (A) For HDL cholesterol, only stratifying by body mass index (BMI) affected the results. When restricting to women with BMI ≥25 kg/m^2, point estimates were in the opposite direction from the main analysis. These estimates, however, are based on small sample sizes and have wide confidence intervals. (B) For C-reactive protein (CRP), the associations observed in the main analysis were attenuated in most sensitivity analyses. Restricting to women with BMI ≥25 kg/m^2 gave similar or stronger results compared to the main analysis, but with wide confidence intervals because of the small sample size.

Table I.

Age and age-standardized characteristics of study participants at time of blood collection by recent and lifetime night shift work history, Nurses' Health Study II, 1996-2001.

	Any Night Shifts in Past Two Weeks[a]		Ever Worked Rotating Night Shifts	
	No (n = 4,760)	Yes (n = 567)	No (n = 1,670)	Yes (n = 3,493)
Age (years), mean (SD)	44.1 (4.5)	43.1 (4.5)	44.1 (4.5)	43.9 (4.5)
Body mass index (kg/m^2), mean (SD)	25.0 (5.0)	26.5 (5.8)	24.6 (4.8)	25.4 (5.1)
Race/ethnicity				
Non-Hispanic white	97.7	96.3	98.3	97.3
Other	2.3	3.7	1.7	2.7
Smoking (past month)				
Nonsmoker	92.9	87.6	93.4	92.0
Smoker	6.9	12.2	6.5	7.8
Missing	0.2	0.3	0.1	0.3
Alcohol consumption, servings per week (past month)				
0	32.0	41.3	34.1	31.8
1-6	57.4	50.8	56.2	57.3
≥7	10.2	7.5	9.5	10.3
Missing	0.4	0.4	0.2	0.6
Physical activity, times per week (past month)				
<1	32.5	32.4	32.8	32.5
1-3	52.4	55.6	51.2	53.0
≥4	14.4	10.6	15.3	13.6
Missing	0.7	1.4	0.8	0.9

Values are standardized to the age distribution of the study population and might not sum to 100% due to rounding.

[a] Includes both permanent and rotating night shifts.

Table II.

Adjusted difference in median lipid levels as a function of recent or lifetime history of night shift work from multivariable quantile regression, Nurses' Health Study II, 1996-2001.

	HDL Cholesterol[a]		LDL Cholesterol[a]		Total Cholesterol[b]		Triglycerides[b]	
	n	Difference, mg/dL (95% CI)	n	Difference, mg/dL (95% CI)	n	Difference, mg/dL (95% CI)	n	Difference, mg/dL (95% CI)
Number of night shifts in past two weeks[c]								
0 nights	1,144	0.0 (Ref)	1,143	0.0 (Ref)	3,215	0.0 (Ref)	2,449	0.0 (Ref)
1-4 nights	81	−4.4 (−7.5, −0.3)	81	6.9 (−4.6, 12.6)	224	1.5 (−3.4, 5.1)	169	0.5 (−7.4, 7.4)
≥5 nights	58	0.8 (−5.0, 2.6)	58	−1.5 (−11.6, 7.1)	135	−5.4 (−11.1, 1.3)	100	−2.0 (−13.6, 10.2)
Years of rotating night shifts during career[d]								
0 years	406	0.0 (Ref)	406	0.0 (Ref)	1,138	0.0 (Ref)	884	0.0 (Ref)
1-5 years	603	0.6 (−2.3, 2.2)	602	−1.4 (−5.0, 3.3)	1,655	−0.5 (−3.5, 3.3)	1,239	1.0 (−2.9, 5.2)
6-9 years	172	−0.8 (−4.6, 3.2)	172	−1.9 (−6.2, 6.1)	445	−3.4 (−9.3, 2.4)	340	−2.3 (−6.1, 5.2)
≥10 years	87	−0.7 (−5.8, 1.6)	87	2.5 (−8.5, 10.4)	224	0.2 (−8.0, 6.6)	178	2.7 (−7.6, 11.1)

Abbreviations: CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[a] Adjusted for age, body mass index, smoking, physical activity, and alcohol consumption.

[b] Adjusted for age, age^2, race/ethnicity, body mass index, smoking, physical activity, and alcohol consumption.

[c] Any type of night shift (e.g., permanent, rotating, infrequent). Model covariates aside from age and race/ethnicity were collected on the questionnaire prior to shift work occurrence.

[d] The following model covariates were taken from reported values at ages 18-22 years: body mass index, smoking, physical activity, and alcohol consumption.

Table III.

Adjusted difference in median triglyceride, C-reactive protein, and fibrinogen levels between nurses working and not working night shifts, from multivariable quantile regression, Nurses' Health Study II, 1996-2001.

	C-Reactive Protein[a]		Fibrinogen[b]	
	n	Difference, mg/L (95% CI)	n	Difference, mg/dL (95% CI)
Number of night shifts in past two weeks[c]				
0 nights	2,744	0.0 (Ref)	415	0.0 (Ref)
1-4 nights	220	−0.0 (−0.2, 0.1)	30	−0.7 (−4.7, 20.6)
≥5 nights	130	−0.1 (−0.3, 0.1)	13	−0.4 (−3.1, 9.4)
Years of rotating night shifts during career[d]				
0 years	963	0.0 (Ref)	152	0.0 (Ref)
1-5 years	1,487	0.1 (0.0, 0.2)	220	1.7 (−1.6, 10.0)
6-9 years	389	0.2 (0.1, 0.4)	71	2.3 (−3.4, 11.4)
≥10 years	183	0.2 (−0.0, 0.4)	15	3.2 (−2.7, 30.1)

Abbreviations: CI, confidence interval.

[a] Adjusted for age, age^2, race/ethnicity, body mass index, smoking, physical activity, and alcohol consumption.

[b] Adjusted for age.

[c] Any type of night shift (e.g., permanent, rotating, infrequent). Model covariates aside from age and race/ethnicity were collected on the questionnaire prior to shift work occurrence.

[d] The following model covariates were taken from reported values at ages 18-22 years: body mass index, smoking, physical activity, and alcohol consumption.