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Shift Work and Biomarkers of Subclinical Cardiovascular Disease: The BCOPS Study

Meghan M. Holst, MSPH[1], **Michael D. Wirth, PhD**[1,2,3], **Anna Mnatsakanova, MS**[5], **James B. Burch, PhD**[1,2,6], **Luenda E. Charles, PhD**[5], **Cathy Tinney-Zara, PhD**[5], **Desta Fekedulegn, PhD**[5], **Michael E. Andrew, PhD**[5], **Tara A. Hartley, PhD**[5], and **John M. Violanti, PhD**[7]

[1]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA.

[2]Cancer Prevention and Control Program, University of South Carolina, Columbia, SC USA.

[3]College of Nursing, University of South Carolina, Columbia, SC, USA.

[5]Biostatistics and Epidemiology Branch, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV, USA.

[6]WJB Dorn VA Medical Center, Columbia, SC, USA.

[7]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University of Buffalo, The State University of New York, Buffalo, NY, USA.

Abstract

Objective: To assess the association of shift work with biomarkers of subclinical cardiovascular disease and examine the moderating role of body mass index (BMI) in a police cohort.

Methods: A cross-sectional analysis was conducted among officers who were categorized as working the day, evening, or night shift. Comparisons with inflammatory biomarkers were performed among shifts using analysis of variance/covariance and further stratified by BMI to assess potential effect modification.

Results: Associations were observed between day and night shift workers for leukocytes, tumor necrosis factor alpha and homocysteine. After BMI stratification, higher c-reactive protein (CRP) levels were observed among evening shift workers with a BMI ≥ 30 kg/m^2 versus the day shift.

Conclusions: Future studies examining prospective changes in these markers will allow for more comprehensive evaluation of their association with shift work.

Keywords

shiftwork; inflammation; cardiovascular disease; police work

Correspondence: Michael D. Wirth, MSPH, PhD, Cancer Prevention and Control Program, University of South Carolina, 915 Greene Street, Room 233, Columbia, SC29208. Phone: (803)-576-5646. Fax: (803)-576-5624. wirthm@mailbox.sc.edu.

INTRODUCTION

Shift work, or working outside the normal working hours, is associated with many adverse health outcomes such as increased psychological and physiological stress, behavioral changes related to coping or adaptation (e.g., smoking, alcohol, diet, physical activity), disturbed socio-temporal patterns, or sleep disturbances that occur due to desynchronized circadian rhythms (1–3). Natural clocks run off different cues from the environment, such as ambient light exposures or meal timing, which help regulate the processes that maintain homeostasis and health (4). Metabolic disturbances resulting from food intake during the night can interrupt the body's regulatory circadian rhythms (4).

Poor quality and quantity of sleep are possible reasons for increased prevalence of health problems in the shift working population. For example, compared to the day shift, night shift workers exhibit more adverse sleep-related events, which are associated with self-reported psychiatric disorders such as depression as well as many physiological diseases (1, 5–9). Abnormal levels of inflammatory markers and the increased risk of hypertension in shift workers could explain the relationship between shift work and CVD (6). Inflammation, the body's natural response to infections and injuries, may be a warning sign for the development of various diseases (13). When there is an injury to the vascular system, the body directs inflammatory cells to the site in order to eliminate the threat and return the tissue to a normal state. Increased levels of other inflammatory markers, such as tumor necrosis factor-alpha (TNF-α), high-sensitivity c-reactive protein (hsCRP) and interleukin-6 (IL-6), were observed in shift workers, which may be explained by disrupted sleep patterns and be precursors of adverse health outcomes (10). Proinflammatory cytokines, such as IL-6 and TNF-α, stimulate hepatic acute phase proteins, such as fibrinogen, hsCRP, and high-density lipoprotein (HDL) cholesterol; therefore, an increase in these levels may indicate that inflammation is present and possibly linked to the pathogenesis of subclinical CVD (11–14).

Levels of fibrinogen, a protein associated with blood clotting, had a positive association with risk of myocardial infarction, CHD, and other CVD-related conditions (11). D-dimer, a fibrin degradation protein and known predictor of ischemic heart disease, is then released to the site stimulating an inflammatory response (15). CRP, a protein cluster produced in response to inflammation, appears to remain constant in individuals without infections or inflammatory diseases, which leads us to believe that elevated levels of this biomarker are predictors in many diseases such as diabetes, acute myocardial infarction, hypertension and CVD (16). Levels between 1 mg/L and 3 mg/L pose a moderate risk for CVD-related events and levels above 3 mg/L present the highest risk (12).

Lipids levels also signal a risk for CVD-related events. High levels of LDL cholesterol and triglycerides, in addition to low levels of HDL cholesterol, occur within a large percentage of CHD patients and are signs of inflammation (13). When inflammation is present, leukocytes accumulate and attempt to remove the damaged cells. Therefore, increased levels of white blood cells (WBCs) in patients with CHD and other CVD-related diseases are observed (17).

E-selectin, endothelin-1, intercellular adhesion molecules (ICAM) and vascular cell adhesion molecules (VCAM), receptors on the endothelium which have been associated with pulmonary arterial hypertension and congestive heart failure, appear to increase in response to inflammation and proinflammatory cytokines such as TNF-α (18). Additionally, heightened levels of homocysteine, an amino acid that is a constituent of many proteins, is positively associated with coronary-related events (19). Abnormal levels of these biomarkers may explain inflammation and health disparities between shift workers. One shift work population susceptible to these changes are police officers.

The Buffalo Cardio-Metabolic Occupational Police Stress (BCOPS) study consists of police officers from Buffalo, New York (20). Results from the BCOPS study have documented various adverse health outcomes associated with working night shifts, including increases in depression, obesity, injuries, and poor sleep quality (3, 20). Increased stress has been associated with CVD risk, the outcome of interest among law enforcement officers (21). Both shift work and an increased prevalence of CVD risk factors, such as obesity, hypertension, metabolic syndrome, and hyperlipidemia, tend to be more common among police officers (22). Therefore, this study examined relationships between shift work and biomarkers of subclinical CVD. Specifically, we hypothesized that officers working night shifts would have increased levels of all examined biomarkers, with an exception for HDL cholesterol in which lower levels signal adverse health conditions.

An increased body mass index (BMI) is associated with night shift work, which may be due in part to the abnormal sleep patterns that are common among shift workers and are associated with metabolic disruption (23, 24). Associations between elevated BMI and CVD risk are well-described; and obesity can induce inflammatory processes that lead to hypertension, CHD, and heart failure (17–26). Thus, BMI was examined as a potential effect modifier.

METHODS

Police officers were recruited from the Buffalo, New York Police Department and attended a single clinic examination date between 2004 and 2009. The majority of officers completed their examination in 2004 or 2005. This study collected data on biomarkers of stress and predictors of CVD, as well as basic demographics, lifestyle behaviors, work experience, anthropometric information (e.g., BMI, waist circumference, abdominal height, blood pressure), psychometric measures (e.g., stress, depression, social support), and shift work from electronic payroll records (20). This analysis utilized participants with non-missing data on demographic, shift work, and CVD marker information (n=360). Exclusions included those who were retired (n=2) and those who were more likely to have acute infections (CRP ≥10 mg/L, n=17; leukocyte count ≥10 ×10^9 cells/L, n=6). The BCOPS study received Institutional Review Board approval from The State University of New York at Buffalo. All officers provided written informed consent.

The officers' daily work schedules were obtained from the City of Buffalo, NY via electronic payroll records. The total hours worked by each officer during the time period spanning from 1994 to date of exam was partitioned into hours worked on the day, evening

and night shift. A dominant shift for each subject was defined as the shift that had the largest percentage of the total hours worked. For example, an officer who worked 20% on day, 70% on the evening, and 10% on night shift is classified as an evening shift worker. The distribution of work start times was examined and consistent with standard shift start times with 99% of the records starting at 07:00 or 08:00 h (for day shift), at 16:00 h (for evening shift), and at 20:00 or 21:00 h (for night shift). For shifts that did not comply with the aforementioned start times the following three categories were used to assign a specific shift to a shift type based on the start time of that shift: day shift (start times between 04:00 and 11:00 h); evening shift (between 12:00 and 19:00 h); and night shift (between 20:00 and 03:00 h). The intervals above were used to capture the 1% of records that did not comply with the standard shift start times mentioned above. This process of summarizing shift work status showed good consistency over 30, 60, or 90 days, and 5 years prior to the clinic date (27).

Blood samples were collected from each officer after they fasted. About 41% indicated they fasted for at least 12 hours. In total, about 96% had fasted for a minimum of 8 hours. Generally, the work schedule followed the pattern of 4 days of work, 4 days off work, 4 days of work, and 3 days off work. Officers were required to undergo clinic examinations on the last day of their off days. Therefore, when the biological samples were collected during the clinic examination, the officers had been off-duty for at least 3 days. Lavender-top vacuum vials with EDTA anti-coagulant were used to collect the blood samples in the morning prior to 08:30. An identification number blinded the blood, serum, or plasma samples and quantity of blood obtained was sufficient for quality control checks. Kaleida laboratories in Buffalo, NY assayed the specimens from a blood lipid panel (cholesterol and triglycerides), chemistry panel, and complete blood count. In addition, the University of Vermont Laboratory for Clinical Biochemistry Research, which has experience in large epidemiologic studies, assessed biomarkers specific to stress, obesity, CVD, and metabolic syndromes including CRP, IL-6, fibrinogen, D-dimer, TNF, and ICAM-1. Quality control for all lab analytes included 5% blind replicate assays.

Covariates from the data set included age, sex, race-ethnicity, marital status, employment information (hours/week, years of service, and rank), blood pressure, health behaviors (e.g. alcohol intake, smoking status, BMI [kg/m^2], and physical activity), and usage of a variety of medications (e.g. anti-hypertensive, hypoglycemic, hypercholesterolemia, fibrate, and nicotinic acid).

Statistical Analysis

Descriptive statistics were compared across shift type using the mean, standard deviation and analysis of variance (ANOVA) tables for continuous variables and frequencies and the Chi-square test for categorical variables. The CVD markers and lipids were log-transformed prior to analyses due to the skewed distributions and the results were then back-transformed to report as means and 95% confidence intervals (CIs). Analysis of variance/covariance (ANOVA/ANCOVA) were used to compare mean levels of all biomarkers across categories of shift work. Variables were considered potential confounders in the multivariable model if they were associated with both the exposure and outcome in the current analyses or were

identified in the literature as such. Associations were adjusted for confounders (age, sex, race/ethnicity) and traditional CVD risk factors (smoking status, BMI, total cholesterol, HDL cholesterol, and triglycerides). BMI was assessed as an interaction term with shift work which we ultimately stratified. Effect modification by BMI was assessed by performing stratified analyses of the association of shift work with CVD biomarkers using the cut point of 30 kg/m^2 (<30 vs ≥30). Statistical significance for all analyses was assessed at the 5% level. However, to assess comparisons between each shift work category, we utilized the Bonferroni correction. All analyses were conducted in SAS v. 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Our final sample size of 360 officers consisted of 266 men and 94 women. The average age of officers in this cohort was 41.4±6.42 years, the majority were White/Hispanic (78%), overweight (mean BMI = 29.3±4.8 kg/m^2) and had at least some level of college education (89%). Overall, about 13% and 10% were on anti-hypertensive or hypercholesterolemia medications, respectively (Table 1). Compared to the day shift, those who worked the night shift were more likely to be White/Hispanic (83% vs. 69%, p <0.01), younger (mean age = 38.8± 6.5 vs 43.1± 6.1 years, p<0.01) and patrol officers (82% vs. 65%, p<0.01).

The least squares mean values of CVD biomarkers and lipids across different categories of shift work are presented in Table 2. When the Bonferroni correction (i.e., 0.05/3) for multiple comparisons was applied, associations were observed between the day and night shift workers for WBC counts (5.36 vs. 5.85 ×10^9/L, p=0.01), and TNF-α (4.52 vs. 5.23 pg/ml, p=0.01), or homocysteine (9.66 vs 8.83 umol/L, p=0.02) concentrations. Adjusted mean IL-6 levels also differed among day and evening workers (1.52 vs 1.93 pg/ml, p<0.01).

Table 3 presents results of the association between shift work and the biomarkers, stratified by BMI. Although all p-values for the interaction between the biomarkers and BMI were not less than 0.10, we decided to stratify the biomarkers by BMI (≥30 kg/m^2 and <30 kg/m^2) because BMI is a known risk factor for CVD.[36–39] Most significant results were found in the larger BMI category; however, a significant p-value (compared to 0.017 calculated by the Bonferroni correction) was found in the day shift versus night shift for TNF-α (4.06 vs 5.04 pg/ml, p<0.01) among those with a BMI <30 kg/m^2.

Among officers with a BMI ≥30 kg/m^2, higher adjusted mean CRP levels were observed among those working evening shifts (3.32 vs. 2.24 mg/L, p=0.01), as well as nights (3.32 vs. 2.09 mg/L, p=0.01) relative to day shifts. Additionally, IL-6 levels were elevated among those working evenings relative to the day shift group (2.41 vs. 1.58 pg/ml, p <0.01). Among officers with BMI ≥ 30 kg/m^2, mean levels of IL-6 and e-selectin were significantly higher in the evening compared to the night shift group (p=0.04 and p=0.02, respectively). Results did not change after adjusting for hypertension status and other relevant factors such as triglyceride, diabetes, blood pressure medication, sleep quality, and systolic and diastolic blood pressure levels.

DISCUSSION

The results from this study indicated that officers on night shifts had higher levels of total leukocytes, TNF- α, and homocysteine compared to the day shift. Higher levels of IL-6 were observed in the evening shift compared to the day shift, however no association was found between the day and night shift groups. After stratifying by BMI and comparing the p-values to the Bonferroni correction, we observed higher levels of CRP in the evening shift group versus the day shift group, as well as the evening shift group versus the night shift group for those with a BMI ≥30 kg/m^2. Without the Bonferroni correction, we found higher levels of IL-6, WBC, and e-selection in the night shift compared to the day shift within the higher BMI category. An elevated BMI is associated with high levels of proinflammatory cytokines and with elevated leukocyte counts (28–32). This could lead to a compounding effect of shift work on inflammatory markers among those with an elevated BMI.

Most scientific literature supports a general relationship between shift work and elevated inflammatory markers, thus increasing risk for CVD (29, 33). Because of the available work history, results of the present study supported shift work as a causative agent for deregulating inflammatory markers. Past studies observed increased levels of TNF-α and leukocytes among shift workers (2, 33–35). Shift workers exhibited higher levels of leukocytes compared to the typical working population, therefore increasing the risk of atherosclerosis and other CVD-related events (10, 36, 37). Another study, in which shift work was self-reported, observed an association between poor sleep and WBC levels in male shift workers (30).

Others have reported associations between shift work and other CVD biomarkers including CRP and IL-6 in an effort to examine the role of inflammation in the pathogenesis of CVD among shift workers. Shift work was associated with increased CRP levels and risk for CVD (10). Sleep deprivation, an adverse health outcome from working shifts, is associated with increased levels of CRP and IL-6, which also suggests a possible link between sleep deprivation, increased levels of inflammatory mediators, and CVD risk (30).

Results from some previous studies differed from the current study. One study reported an association between shift work and IL-6, CRP, and leukocytes, but not TNF-α in a general shift work population. The authors reasoned that gene expression of TNF-α is primarily monocytic, and monocyte counts did not vary between shifts in that study (33). Another study did not find a relationship between shift work groups and leukocytes, TNF-α, and IL-6 in a general shift work population, even after observing a significant difference in sleep patterns (29). Those researchers suggested that sleep deprivation may not always cause the immune system to become compromised. In the present study, higher homocysteine levels were found in the day shift group compared to the other shifts, which is inconsistent with results from other studies. Elevated homocysteine levels among shift workers have been previously reported in general shift workers and shift workers at an electric company (33, 38). From a study of long-haul bus drivers working shifts, factors such as shift schedule, work duration, coping strategies, meal timing, or other factors may help explain the discrepancies between this and other studies (39).

Concerning shift work and lipid markers, one meta-analysis suggests there is an increase in total cholesterol in those who are exposed to a minimum of 20 years of shift work (40). The median years of service in our population is 14.9 years overall and 10.9 years for night shift workers, which may not have been long enough to detect an association between shift work and total cholesterol; however, total lifetime shift work history was not factored into our study. HDL cholesterol trended the same as total cholesterol. A future longitudinal study would be appropriate to determine a more concrete relationship between cholesterol and shift work. Increased levels of triglycerides, another lipid biomarker, have been previously associated with shift workers (41, 42). Additionally, one study found increased levels of triglycerides and low levels of HDL cholesterol in shift workers, however, the participants were not asked to fast before samples were drawn which may be further evidence that a dietary factor is responsible for fluctuations in lipid biomarkers (43).

Strengths of this study include the use of quantitative measures of exposure and outcome. Each participant's electronically recorded shift work was quantified, thereby allowing for objective and accurate classification of shift work status. Another strength is the generalizability to other high-stress, shift working occupations such as the military. Clinically obtained biomarkers were used to assess CVD risk factors instead of self-reported data which may avoid reporting bias, and assays were performed by two accredited organizations: The University of Vermont Laboratory for Clinical Biochemistry Research and Kaleida Laboratories in Buffalo, NY. Additionally, information on potential confounders were included in the analysis. Although rank appears to be a potential confounder, we did not adjust for it because it is highly correlated with age. Including this variable in the model did not change our results.

One general limitation is the demographics of our population. Most subjects were White males with an average age of 41, therefore, results from our study may not be particularly applicable to other demographics from different regions across the United States. Disrupted sleep patterns are often blamed for irregular levels of inflammatory markers, and some previous studies assessing the relationship between shift work and inflammatory biomarkers have evaluated the role of sleep quality or quantity, which was not selected as a confounder or effect modifier in our analysis (30). Additionally, causality cannot be inferred due to the cross-sectional nature of the analysis. Some information bias may have occurred due to the use of BMI cutpoints. The mean BMI in this study population was 29.3 kg/m^2, thus a cut point of 30 kg/m^2 was used, which grouped "underweight", "normal", and "overweight" officers together for comparison against "obese" individuals. Selective survival may play a role is the reasoning between the higher risk of CVD found in those working the evening shift than the night shift. The majority of night shift workers may stay on the shift because they are physically and mentally able to, while others are moved to the evening shift due to miscellaneous physical or psychological concerns; this may then result in the evening group with a higher risk of CVD than the officers working the night shift (36). Although we did adjust for Bonferroni, this was done within each outcome (i.e., adjusted for three comparisons between day, evening, and night shift groups) and not across all outcomes (i.e., three comparisons times 20 outcomes). Many of these outcomes have rarely or never been examined with respect to shift work and were exploratory in nature. Lastly, the results should be interpreted with caution when considering biological significance versus statistical

significance. Although some results were statistically significant, the effect estimates were small which may indicate a lack of biological significance. At the same time, some values were well within normal limits. For example, mean WBC counts, regardless of shift type, fell between 3 and 11 × 10^9 cells/L. However, it should be noted that increases in certain chronic diseases (e.g., CVD) have been observed for those with elevated WBCs that have been within this normal range of 3 to 11 × 10^9 cells/L (44, 45).

In conclusion, several CVD biomarkers were elevated among police officers working nights compared to those on day shifts, consistent with the results from some previous studies. Increased levels of inflammatory markers in response to shift work may mediate the increased risks for CVD that have been observed among shift workers. Because night work in police departments is a necessity, these and related findings suggest that workplace administrators might consider worker education on risk factors and early signs of CVD and other vascular-related diseases. Future studies utilizing a longitudinal design may be particularly beneficial in elucidating causal pathways and developing effective intervention or disease prevention strategies. Additionally, larger sample sizes and data from different geographic locations and populations may allow for greater generalizability.

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Table 1:

Demographic, lifestyle, and other characteristics of the study population, by shift work status in the past year.

Characteristic	All (n=360)	Day (n=181, 50%)	Evening (n=97, 27%)	Night (n=82, 23%)	P-value
			Mean ± SD		
Age (years)	41.4±6.42	43.1 ± 6.05	40.5 ±6.09	38.8 ± 6.53	<0.01
Years of service	14.9±6.85	16.8 ± 6.42	14.6 ± 6.86	10.9 ± 5.99	<0.01
Alcohol intake	5.21±8.52	5.26 ±10.0	5.99 ± 7.99	4.15 ± 4.56	0.36
Physical activity	21.5±17.9	20.4 ± 17.1	23.6 ± 20.1	21.4 ± 17.0	0.38
Body mass index (kg/m^2)	29.3±4.76	28.8 ± 4.97	30.0 ± 4.28	29.4 ± 4.77	0.11
Hours of work per week	33.2±5.25	32.2 ± 5.08	35.0 ± 5.06	33.2 ± 5.31	<0.01
Systolic BP, mmHg	120±12.0	120 ± 12.7	121 ± 11.4	121 ± 11.3	0.67
Diastolic BP, mmHg	77.8±9.99	77.1 ± 10.35	78.6 ± 8.61	78.7 ± 10.7	0.32
			N (%)		
Race/ethnicity					<0.01
White/Hispanic	279 (78.4)	124 (69.3)	87 (91.6)	68 (82.9)	
African American	77 (21.6)	55 (30.7)	8 (8.4)	14 (17.1)	
Education					0.17
≤ 12 years/GED	38 (10.6)	20 (11.1)	10 (10.4)	8 (9.8)	
College < 4 yrs	205 (57.3)	113 (62.8)	51 (53.1)	41 (50.0)	
College ≥ 4 yrs	115 (32.1)	47 (26.1)	35 (36.5)	33 (40.2)	
Marital status					0.15
Single	44 (12.3)	21 (11.6)	8 (8.4)	15 (18.3)	
Married	262 (73.2)	134 (74.0)	76 (80.0)	52 (63.4)	
Divorced	52 (14.5)	26 (14.4)	11 (11.6)	15 (18.3)	
Police rank					<0.01
Patrol officer	255 (71.0)	118 (65.2)	70 (72.9)	67 (81.7)	
Serg/Lieut/Captain	49 (13.6)	21 (11.6)	13 (13.5)	15 (18.3)	
Detective/Exec/Other	52 (14.5)	42 (23.2)	13 (13.5)	0 (0.0)	
Smoking status					0.17
Current	58 (16.3)	27 (15.2)	12 (12.5)	19 (23.2)	
Former	83 (23.3)	48 (27.0)	20 (20.8)	15 (18.3)	
Never	215 (60.4)	103 (57.9)	64 (66.7)	48 (58.5)	
Hypertension					0.20
No	278 (77.2)	134 (74.0)	81 (83.5)	63 (76.8)	
Yes	82 (22.8)	47 (26.0)	16 (16.5)	19 (23.2)	
Anti-hypertensive meds					0.02
No	313 (87.2)	149 (82.3)	89 (92.7)	75 (91.5)	
Yes	46 (12.8)	32 (17.7)	7 (7.3)	7 (8.5)	
Hypoglycemic meds					0.21
No	352 (98.1)	175 (96.7)	95 (99.0)	82 (100.0)	
Yes	7 (1.95)	6 (3.3)	1 (1.0)	0 (0.0)	

Characteristic	All (n=360)	Day (n=181, 50%)	Evening (n=97, 27%)	Night (n=82, 23%)	P-value
Hypercholesterolemia medication					0.51
No	322 (89.7)	159 (87.9)	88 (91.7)	75 (91.5)	
Yes	37 (10.3)	22 (12.2)	8 (8.3)	7 (8.5)	
Fibrate medication					0.01
No	354 (98.6)	181 (100.0)	92 (95.8)	81 (98.8)	
Yes	5 (1.39)	0 (0.0)	4 (4.2)	1 (1.2)	
Nicotinic acid medication					1.00
No	358 (99.7)	180 (99.5)	96 (100.0)	82 (100.0)	
Yes	1 (0.28)	1 (0.5)	0 (0.0)	0 (0.0)	

Results and summary p-values were obtained from ANOVA (continuous variables) and the Chi-square test (categorical variables).

Table 2:

Adjusted mean values and 95% confidence intervals of CVD biomarkers and lipids across categories of shift work in the past year.

Outcomes	Day (n=181)	Evening (n=97)	Night (n=82)	P(D v N)[a]	P(D v E)[a]	P(E v N)[a]	Interaction By BMI[c]
WBC (x 10^9 cells/L)	5.36 (5.18-5.54)	5.73 (5.48-5.99)	5.85 (5.58-6.14)	*0.01	0.03	0.52	0.09
CRP (mg/L)	1.55 (1.35-1.79)	1.77 (1.48-2.13)	1.67 (1.38-2.04)	0.56	0.28	0.66	0.12
Fibrinogen (mg/dL)	299 (289-310)	295 (281-310)	306 (291-322)	0.49	0.69	0.30	0.52
Interleukin-6 (pg/mL)	1.52 (1.38-1.66)	1.93 (1.71-2.18)	1.77 (1.56-2.02)	0.06	*<0.01	0.31	0.14
TNF (pg/mL)	4.52 (4.25-4.81)	4.92 (4.53-5.33)	5.23 (4.79-5.7)	*0.01	0.12	0.29	0.30
Endothelin-1 (pg/mL)	1.59 (1.54-1.66)	1.62 (1.54-1.71)	1.60 (1.52-1.69)	0.92	0.64	0.73	0.08
E-Selectin (ng/mL)	41.5 (39.1-44.0)	43.2 (39.9-46.7)	40.2 (36.9-43.7)	0.55	0.45	0.20	0.19
VCAM (ng/mL)	735 (703-769)	769 (724-816)	742 (696-790)	0.83	0.26	0.41	0.12
Homocysteine (umol/L)	9.66 (9.28-10.1)	9.01 (8.54-9.50)	8.83 (8.34-9.35)	*0.02	0.05	0.60	0.89
D-Dimer (ug/mL)	0.23 (0.21-0.26)	0.23 (0.21-0.26)	0.25 (0.22-0.28)	0.50	0.98	0.53	0.64
ICAM-1	233 (219-249)	220 (202-240)	217 (198-238)	0.22	0.31	0.83	0.51
Total chol. (mg/dL)[b]	204 (199-210)	199 (191-206)	197 (189-205)	0.14	0.27	0.71	0.95
HDL chol. (mg/dL)[b]	43.5 (41.6-45.4)	45.1 (42.6-47.8)	44.4 (41.7-47.2)	0.62	0.34	0.68	0.91
LDL chol. (mg/dL)[b]	130 (125-135)	128 (121-135)	126 (119-134)	0.45	0.69	0.73	0.65
Triglycerides (mg/dL)[b]	111 (100-122)	95.8 (84.3-108)	98.9 (86.3-113)	0.21	0.09	0.73	0.74

The outcome variable was first log-transformed then back-transformed for reporting.

Models adjusted for age, gender, race/ethnicity, smoking status, BMI, total cholesterol, HDL cholesterol, and triglycerides

[a] P-values for multiple comparisons between categories of shift work.

[b] Model adjusted for age, gender, race/ethnicity, smoking, and BMI.

[c] Interaction between shift work and BMI

* Signifies p-values less than .017 according to the Bonferroni correction.

Abbreviations: WBC – white blood cells, CRP – C-reactive protein, TNF – tumor necrosis factor-α, VCAM – vascular cell adhesion molecule, ICAM – intercellular adhesion molecule, D – day, N – night, E – evening

Table 3.

Adjusted mean values and 95% confidence intervals of biomarkers across categories of shift work stratified by BMI.

Outcomes	Day (n=181)	Evening (n=97)	Night (n=82)	p-value[a]	P (D v N)[b]	P(D v E)[b]	P (E v N)[b]
BMI <30 kg/m^2							
WBC (x 10^9 cells/L)	5.33 (5.09-5.59)	5.86 (5.50-6.26)	5.76 (5.38-6.17)	0.06	0.08	0.03	0.70
CRP (mg/L)	1.22 (0.99-1.48)	1.16 (0.88-1.53)	1.41 (1.06-1.89)	0.58	0.43	0.81	0.32
Fibrinogen (mg/dL)	295 (281-310)	286 (267-305)	306 (285-328)	0.34	0.42	0.47	0.14
Interleukin-6 (pg/mL)	1.46 (1.28-1.66)	1.67 (1.39-2.01)	1.68 (1.39-2.04)	0.41	0.25	0.26	0.95
TNF (pg/mL)	4.06 (3.73-4.43)	4.76 (4.23-5.36)	5.04 (4.44-5.71)	0.02	*0.01	0.05	0.50
Endothelin-1 (pg/mL)	1.57 (1.5-1.65)	1.52 (1.43-1.62)	1.58 (1.48-1.69)	0.64	0.90	0.44	0.40
E-Selectin (ng/mL)	38.2 (25.3-41.3)	38.6 (34.7-43.0)	37.8 (33.7-42.4)	0.96	0.89	0.88	0.78
VCAM (ng/mL)	720 (682-761)	806 (747-869)	777 (717-841)	0.07	0.15	0.03	0.50
Homocysteine (umol/L)	9.40 (8.96-9.87)	8.76 (8.20-9.37)	8.73 (8.13-9.37)	0.17	0.11	0.11	0.93
D-Dimer (ug/mL)	0.22 (0.20-0.25)	0.22 (0.19-0.26)	0.25 (0.21-0.29)	0.57	0.34	0.98	0.36
ICAM-1	233 (218-249)	219 (200-239)	226 (205-249)	0.58	0.63	0.30	0.61
Total chol. (mg/dL)[c]	203 (196-210)	193 (183-203)	195 (184-205)	0.30	0.24	0.15	0.82
HDL chol. (mg/dL)[c]	47.2 (44.8-49.7)	48.2 (44.9-51.8)	47.5 (44.0-51.2)	0.90	0.90	0.64	0.76
LDL chol. (mg/dL)[c]	132 (126-138)	121 (112-130)	124 (115-133)	0.14	0.17	0.06	0.67
Trig. (mg/dL)[c]	87.1 (76.9-98.8)	83.7 (70.4-99.6)	87.4 (72.7-105)	0.92	0.98	0.73	0.72
BMI≥30 kg/m^2							
WBC (x 10^9 cells/L)	5.41 (5.15-5.69)	5.57 (5.23-5.94)	5.95 (5.56-6.37)	0.10	0.03	0.49	0.16
CRP (mg/L)	2.24 (1.86-2.7)	3.32 (2.63-4.2)	2.09 (1.63-2.69)	0.01	0.67	*0.01	*0.01
Fibrinogen (mg/dL)	306 (289-324)	311 (290-334)	305 (283-330)	0.91	0.98	0.71	0.71
Interleukin-6 (pg/mL)	1.58 (1.41-1.79)	2.41 (2.08-2.81)	1.92 (1.63-2.25)	<0.01	0.07	*<0.01	0.04
TNF (pg/mL)	5.24 (4.82-5.69)	5.31 (4.78-5.89)	5.57 (4.98-6.23)	0.69	0.41	0.86	0.53
Endothelin-1 (pg/mL)	1.63 (1.53-1.73)	1.81 (1.68-1.95)	1.63 (1.5-1.77)	0.08	0.97	0.04	0.06
E-Selectin (ng/mL)	45.9 (41.9-50.3)	53.1 (47.3-59.6)	43.7 (38.6-49.4)	0.05	0.54	0.06	0.02
VCAM (ng/mL)	753 (699-811)	733 (667-804)	696 (630-770)	0.48	0.23	0.66	0.46
Homocysteine (umol/L)	10.2 (9.55-10.9)	9.15 (8.39-9.97)	8.98 (8.18-9.85)	0.06	0.03	0.06	0.76

Outcomes	Day (n=181)	Evening (n=97)	Night (n=82)	p-value[a]	P (D v N)[b]	P(D v E)[b]	P (E v N)[b]
D-Dimer (ug/mL)	0.26 (0.22-0.30)	0.25 (0.21-0.30)	0.25 (0.20-0.30)	0.92	0.71	0.78	0.92
ICAM-1	232 (205-263)	226 (193-265)	206 (173-244)	0.54	0.28	0.80	0.42
Total chol. (mg/dL)[c]	207 (197-217)	208 (196-220)	198 (185-211)	0.47	0.29	0.89	0.26
HDL chol. (mg/dL)[c]	38.7 (35.8-41.9)	40.6 (36.8-44.9)	40.0 (35.9-44.6)	0.75	0.62	0.46	0.83
LDL chol. (mg/dL)[c]	128 (119-137)	138 (126-149)	128 (116-140)	0.40	0.97	0.22	0.25
Triglycerides (mg/dL)[c]	153 (131-179)	124 (102-151)	120 (97.2-148)	0.13	0.07	0.11	0.81

Model adjusted for age, gender, race/ethnicity, smoking status, total cholesterol, HDL cholesterol, and triglycerides.

[a]P-values obtained from ANOVA/ANCOVA.

[b]P-values for multiple comparisons between categories of shift work.

[c]Model adjusted for age, gender, race/ethnicity, and smoking.

*Signifies p-values less than .017 according to the Bonferroni correction.

Abbreviations: WBC – white blood cells, CRP – C-reactive protein, TNF – tumor necrosis factor-α, VCAM – vascular cell adhesion molecule, ICAM – intercellular adhesion molecule, D – day, N – night, E – evening