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Leptin, Adiponectin, and Heart Rate Variability Among Police Officers

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Abstract

Objectives—Police officers have a high prevalence of cardiovascular disease (CVD). Reduced heart rate variability (HRV) is known to increase CVD risk. Leptin and adiponectin may be related to CVD health. Therefore, our objective was to investigate the relationship between these variables and HRV.

Methods—Leptin and adiponectin levels were measured in 388 officers from the Buffalo Cardio-Metabolic Occupational Police Stress study. HRV was assessed according to methods published by the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology for measurement and analysis of HRV. Mean values of high-frequency (HF) and low-frequency (LF) HRV were compared across tertiles of leptin and adiponectin using analysis of variance and analysis of covariance; trends were assessed using linear regression models.

Results—Leptin, but not adiponectin, was significantly and inversely associated with HRV. Body mass index (BMI) and percent body fat significantly modified the association between leptin and LF (but not HF) HRV. Among officers with BMI < 25 kg/m^2, leptin was not significantly associated with HRV. However, among officers with BMI ≥ 25 kg/m^2, leptin was inversely associated with HRV, after adjustment for age, gender, and race/ethnicity; HF HRV, $P = 0.019$

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and LF HRV, $P < 0.0001$. Similarly, among officers with percent body fat ≥ 25.5%, leptin and LF HRV showed significant, inverse associations (adjusted $P = 0.001$).

Conclusions—Leptin levels were inversely associated with LF HRV, especially among officers with increased adiposity. Increased leptin levels may be associated with CVD-related health problems.

Adiponectin and leptin are protein hormones that are primarily secreted by adipocytes. Adiponectin has an antiinflammatory role and is generally seen as providing many health benefits (Kwon and Pessin, 2013). It stimulates fatty acid oxidation, acts on the central nervous system to influence the control of body weight, protects endothelial cells and vascular function, and regulates metabolism and insulin sensitivity (Hopkins et al., 2007; Kwon and Pessin, 2013; Swarbrick and Havel, 2008; Tabak et al., 2009). Leptin is one of the primary hormones involved in regulating energy intake and expenditure in the reproductive, renal, and cardiovascular systems (Ren, 2004) and in controlling aspects of bone remodeling (Elefteriou et al., 2005). Increased levels of leptin have been shown to be directly associated with systemic inflammation, immune-mediated disorders, and cerebrovascular and cardiovascular disease (CVD; Ble et al., 2005; Hasan-Ali et al., 2011; Liu et al., 2010; Vadacca et al., 2011). Increased leptin levels are known to adversely affect autonomic nervous system (ANS) function (Paolisso et al., 2000).

Heart rate variability (HRV) reflects the beat-to-beat variability in heart rate and the heart's ability to quickly respond to changing environments (Acharya et al., 2006). It is a noninvasive marker of the renin–angiotensin–aldo-sterone system, the cardiovascular control system, and the ANS (Rolim et al., 2013). The ANS regulates the operation of the internal organs to support the activity of the body and is composed of (a) the sympathetic nervous system, which prepares the body overall for activity, and (b) the parasympathetic nervous system, which has restorative functions such as digestion and slowing of the heartrate (Pocock and Richards, 1999). Reduced HRV has been shown to be associated with ongoing subclinical inflammation (Haensel et al., 2008), diabetes mellitus (Malpas and Maling, 1990), and an increased risk of CVD morbidity and mortality (Chandra et al., 2012; Reed et al., 2005; Tsuji et al., 1996).

Cardiovascular disease is the number one cause of morbidity and mortality in the United States (Kung et al., 2008), and studies show that police officers experience a greater burden of CVD than persons in the general population (Franke et al., 2002; Zimmerman, 2012). Police officers also have a high prevalence of obesity (Alasagheirin et al., 2011). Because of the higher obesity and CVD prevalence, it is important to identify other factors that may be associated with subclinical CVD, such as HRV, in this occupational cohort. Levels of leptin have been shown to be associated with decreased cardiac vagal tone (Flanagan et al., 2007; Jung et al., 2012; Matsumoto et al., 2003; Paolisso et al., 2000). The relationship between adiponectin and HRV is less clear. In one study, adiponectin levels were not related to any HRV parameters (Jung et al., 2012). However, low levels of adiponectin were associated with cardiac sympathetic overactivity in men with Type 2 diabetes mellitus in another study (Takahashi et al., 2007).

In their review, Elmquist et al. (1998) reported that the total absence of leptin causes morbid obesity and that leptin exerts its effects through several central nervous system pathways (Elmquist et al., 1998). A recent cross-sectional study of leptin and ANS activity found inverse associations between leptin levels and HRV after adjustment for several CVD risk factors including body mass index (BMI; Pieterse et al., 2014). This result suggests that the influence of leptin on ANS activity may not be secondary to obesity. Our study seeks to take into consideration and expand on these findings by using a detailed parameterization of HRV, available from resting data, and determining whether measures of adiposity modify associations of leptin and adiponectin with HRV. Therefore, the primary objective of this study was to investigate the association of adiponectin and leptin with HRV. Higher levels of leptin and lower levels of adiponectin are generally found in individuals with higher levels of obesity (Sztajzel et al., 2009), and women are more likely to have higher levels of obesity (Ogden et al., 2006). Therefore, secondary objectives were to determine if gender, BMI, percent body fat, and other measures of adiposity (waist circumference and abdominal height) significantly modify this association. We hypothesized that there would be an inverse association between leptin and HRV and a positive association between adiponectin and HRV. We also hypothesized that among officers with higher adiposity levels, the association between leptin and HRV would be stronger and that between adiponectin and HRV would be attenuated.

METHODS

Study design and participants

The Buffalo Cardio-Metabolic Occupational Police Stress study, a cross-sectional comprehensive examination of the health consequences of stress in law enforcement officers, began in 2004. Between June 2004 and October 2009, ~710 police officers employed at the Buffalo, New York Police Department were invited to participate in this study. Data were collected at the Center for Health Research, School of Public Health and Health Professions, University at Buffalo, State University of New York (Violanti et al., 2006). The State University of New York at Buffalo and the National Institute for Occupational Safety and Health Internal Review Boards approved the study, and informed consent was obtained from all participants. Although 464 officers consented to participate, 448 officers had complete information on leptin and adiponectin levels and 447 officers completed an ECG to obtain HRV data. Of the 447 officers, those who reported having a physician-diagnosed history of irregular heart rate (n = 25) or had significant evidence of irregular beats or abnormal QRS intervals (n = 32) were excluded from these analyses, resulting in 390 officers with adequate HRV measurements. Two of these 390 officers did not have information for leptin or adiponectin. The final sample size for these cross-sectional analyses of leptin and adiponectin with HRV was 388 officers, 94 women and 294 men.

Clinical examination

Each officer in this study had all measurements obtained on the same day. The officers were instructed to abstain from eating or drinking anything but water, strenuous physical exercise, and use of tobacco after 10 p.m. on the night before the day of examination. All officers

were given a standardized breakfast of 280 calories around 8:30 a.m. after blood specimens were collected and before other components of the examination were performed.

Assessment of leptin and adiponectin

Leptin and adiponectin were analyzed using fasting serum at the University of Vermont. Adiponectin was analyzed on the Millipore Multiplex Panel A and leptin on the Millipore Multiplex Panel B. The Millipore panels use Luminex® technology. The detectable range for leptin and adiponectin is approximately 16 to 250,000 pg/ml. The normal ranges, as specified by the assay manufacturers are 1,000–20,000 ng/ml for adiponectin and 1,100–12,000 pg/ml in males and 3,800–77,000 pg/ml in females for leptin. The interassay coefficient of variation ranges for leptin is 5.4–7.2% and for adiponectin 7.2–9.0%.

Assessment of HRV

Measurement of HRV was performed according to standard methods published by the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology for measurement and analysis of HRV (Camm et al., 1996). During the carotid ultrasound examination, ECG voltages were sampled at 2,000 Hz and captured digitally using a research quality data acquisition system designed for HRV measurement, storage, and analysis. The measurement system was provided by the Biopac Systems MP100 system/software along with an accompanying ECG Amplifier (C series), appropriate ECG leads, cables, electrodes, and a compatible PC for data processing and recording. Complete details of the assessment of HRV have been published elsewhere (Andrew et al., 2013).

Assessment of covariates

Demographic characteristics, lifestyle behaviors, and medical history and medication were obtained from all officers through self- and interviewer-administered questionnaires. Officers were asked how often they consumed alcoholic beverages with one drink defined as a 12-oz can or bottle of beer, one medium glass of wine, or one shot of liquor. The total number of drinks consumed per week was used. Officers reported their smoking status as current, former, or never. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Abdominal height was measured with the officer in the supine position. A caliper was used to measure the midsection, one inch above the iliac crests. Three measurements were taken (to the nearest 0.1 cm), and the average value was used. Waist circumference was also obtained from the average of three measurements that were within 0.5 cm of each other. Trained and certified technicians from the Osteoporosis Research Center at the University at Buffalo measured percent body fat using the dual-energy X-ray absorptiometry (DEXA; DXA Hologic QDR 4500A machine; Hologic, Waltham, MA). The DEXA scanner uses a very low dose of radiation and also measures skeletal density, total body fat, and lean body mass. Blood pressure was determined using the average of the second and third of three separate measurements of resting systolic and diastolic blood pressure obtained with a standard sphygmomanometer.

Physical activity during the previous 7 days was obtained with the Seven-Day Physical Activity Recall questionnaire used in the Stanford Five-City Project (Sallis et al., 1985). Venous blood was drawn at the clinic during the morning hours from officers who had

fasted for the previous 12 h. Serum was removed from the blood after centrifugation, and aliquots were frozen at −80°C. Laboratory analyses of glucose and lipids were measured by standard laboratory techniques on the Beckman Coulter LX20 clinical chemistry analyzer.

Metabolic syndrome was defined using the criteria from the National Cholesterol Education Program Adult Treatment Panel III guidelines that include recent modifications from the American Heart Association and the National Heart, Lung, and Blood Institute (Grundy et al., 2005). Metabolic syndrome includes five components: abdominal obesity, hypertension, reduced HDL-C, elevated triglycerides, and glucose intolerance (see definitions in Grundy et al., 2005). Officers having three or more components were considered to have metabolic syndrome. Diabetes was defined as having a fasting blood glucose level of ≥126 mg/dl or taking diabetic medication. Hypertension was defined as having a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure of ≥90 mm Hg, or a self-report of physician-diagnosed hypertension and antihypertensive treatment.

Statistical methods

Univariate analysis was used to describe characteristics of the study participants. Because of the skewed distributions, leptin and HRV were log-transformed prior to analyses, and the results were back-transformed for reporting as means and 95% confidence intervals (CIs). Mean values of HRV were obtained across tertiles of leptin and adiponectin using analysis of variance. *P*-values for trends were obtained from linear regression analysis. A value of $P < 0.05$ was considered statistically significant. Variables were chosen as potential confounders and included in the multivariate models based on their roles as confounding variables in published studies or if they were significantly associated with both the independent and dependent variables in the current study. Analysis of covariance was used to examine the effect of adjustment for several covariates (age, gender, and race/ethnicity) on the relationship of leptin and adiponectin with HRV. Gender, BMI, percent body fat, waist circumference, and abdominal height were assessed for effect modification. When stratifying on variables that were significant effect modifiers, the cut points were assigned as follows: BMI (25 kg/m^2), percent body fat (25.5%), waist circumference (95 cm), and abdominal height (20 cm). As there is not a single, clinically meaningful cut-point for each of the above variables for both genders (except for BMI), we chose cut-points that would define high and low values reasonably well for both men and women. SAS version 9.3 was used to analyze these data (SAS, 2008).

RESULTS

Descriptive statistics of all variables are presented in Table 1. The mean (± SD) age of all officers was 41.7 ± 8.0 with a range of 21–70 years. The majority of officers were male (75.8%) and White (78.2%). Women had a significantly higher mean level of percent body fat when compared with men (30.7% ± 5.9% vs. 23.8% ± 5.1%, $P < 0.0001$), whereas the reverse was true for BMI, abdominal height, and waist circumference (all $P < 0.0001$). Men had a slightly higher but nonsignificant mean level of low-frequency (LF) HRV ($P = 0.217$), whereas women had significantly higher mean levels of high-frequency (HF) HRV ($P = 0.004$), leptin ($P < 0.001$), and adiponectin ($P < 0.001$).

Age-adjusted correlation coefficients and mean values for the relationship between selected characteristics and HRV were obtained (data not shown). All of the anthropometric variables, triglycerides, and insulin were inversely and significantly correlated with HF HRV, whereas physical activity score was positively correlated with both HF and LF HRV. Officers who were hypertensive had a significantly lower mean HRV value (both LF and HF) when compared with those who were not hypertensive: HF HRV = 105.8, 95% CI = 83.7–133.6 vs. 156.8, 95% CI = 138.4–177.5, $P = 0.004$. Officers who had metabolic syndrome also had a significantly lower mean HRV value (both LF and HF) when compared with those who did not have metabolic syndrome: HF HRV = 101.9, 95% CI = 8.5–125.9 vs. 159.8, 95% CI = 141.0–181.1, $P < 0.001$.

The associations of selected characteristics with leptin and adiponectin were also assessed, and the results are shown in Table 2. All of the anthropometric variables, total cholesterol, insulin, and HOMA were positively and significantly correlated with leptin. Officers who were hypertensive and those who had metabolic syndrome had significantly higher mean levels of leptin when compared with those who did not have either of those conditions. Age and HDL cholesterol were positively and significantly correlated with adiponectin. In contrast, all of the anthropometric variables, triglycerides, glucose, and insulin showed significant, inverse correlations with adiponectin. Officers who were hypertensive or had metabolic syndrome had significantly lower mean levels of adiponectin when compared with those who did not have either of those conditions.

In Table 3, the mean values and 95% CIs of both HF and LF HRV are compared across tertiles of leptin. After adjustment for age, gender, and race/ethnicity, the associations between leptin and both HF HRV and LF HRV were inversely, statistically significant, $P = 0.028$ and 0.001, respectively. The associations between adiponectin and HRV were not significant, and thus, these results were not shown in the tables.

Gender did not modify the association between leptin and HRV, but BMI significantly modified the association between leptin and LF HRV, interaction $P = 0.002$. In Table 4, the mean values and 95% CIs of HRV are compared across tertiles of leptin while stratifying by BMI. Among officers with BMI < 25 kg/m^2, the association between leptin and HRV was not significant. However, among officers with BMI ≥ 25 kg/m^2, the association between leptin and HRV was statistically significant. As leptin levels increased, mean values of HF and LF HRV decreased after adjustment for age, gender, and race/ethnicity; HF HRV, $P = 0.019$, and LF HRV, $P < 0.0001$.

In Table 5, the mean values and 95% CIs of HRV are compared across tertiles of leptin, stratified by percent body fat. Percent body fat significantly modified the association between leptin and LF HRV, interaction $P = 0.010$. The results were similar to those observed with the BMI-stratified analyses. Among officers with ±25.5% body fat, the association between leptin and HRV was not significant. However, among officers with ≥25.5% body fat, leptin was inversely related to LF HRV (but not HF HRV). Before risk-factor adjustment, strong, monotonic trends were observed, $P < 0.001$, and the association was only slightly attenuated after adjustment for age, gender, and race/ethnicity, $P = 0.001$.

Waist circumference and abdominal height also significantly modified the association between leptin and LF HRV, interaction $P = 0.015$ and 0.005, respectively. The results mirrored those presented in Tables 4 and 5, and thus, these data are not shown. Leptin was significantly and inversely associated with LF HRV but not HF HRV, among officers with higher levels of central adiposity. These results showed very little attenuation after adjustment for age, gender, and race/ethnicity.

DISCUSSION

The goals of this cross-sectional study were to investigate associations of leptin and adiponectin with HRV. In this cohort of law enforcement officers, leptin levels were inversely and significantly associated with LF HRV among all officers, and particularly among officers with BMI ≥ 25 kg/m^2, percent body fat ≥ 25.5%, and higher levels of abdominal adiposity. The associations between leptin and HRV did not differ significantly by gender.

We identified several studies that investigated the direct association between leptin and HRV and other studies that assessed the association between obesity and HRV, as it has been long established that leptin is directly related to body weight (Frederich et al., 1995; Matsumoto et al., 2003). Results on the relationship between leptin and HRV were mixed. Sztajzel et al. (2009) investigated the alterations of cardiac autonomic function in groups of patients with various levels of BMI. Their results showed that leptin was negatively correlated with most HRV indices with the exception of HF HRV. In addition, LF HRV was lower in both obese and morbidly obese patients, whereas HF HRV was lower only in morbidly obese patients, when compared with persons of normal weight. Investigators who studied autonomic function in obese and nonobese individuals reported lower HRV values in the obese participants when compared with those who were not obese and negative associations between weight and HRV (Matsumoto et al., 2003; Petretta et al., 1995; Piccirillo et al., 1996). A recently published study conducted on the same cohort of officers as our study reported inverse associations between central adiposity and HRV (Andrew et al., 2013). Another study reported lower expressions of HRV with greater abdominal-to-peripheral body fat distribution and greater total adiposity (Christou et al., 2004).

Our results with leptin were not consistent with other studies. Flanagan et al. (2007) reported significant, positive correlations between leptin and LF (but not HF) HRV among healthy young women; however, these correlations were not significant among men. In a study of nonobese, nonsmoking, normotensive young Italian males, LF HRV progressively and significantly increased from the first to the fourth quartile of leptin, whereas HF HRV showed a significant decline (Paolisso et al., 2000). Among obese and nonobese males with acute myocardial infarction, leptin was positively and significantly associated with LF HRV, whereas the association with HF HRV was not statistically significant (Piestrzeniewicz et al., 2008).

Persons who are healthier overall and have a lower BMI tend to have higher levels of adiponectin (Kwon and Pessin, 2013; Piestrzeniewicz et al., 2008; Takahashi et al., 2007). In our study, associations between adiponectin and HRV were not statistically significant

among the officers. These findings were supported by several studies (Piestrzeniewicz et al., 2008; Sztajzel et al., 2009; Takahashi et al., 2007). In a cross-sectional study, adiponectin was not related to any HRV variables among obese and nonobese males with acute myocardial infarction (Piestrzeniewicz et al., 2008). Takahashi et al. (2007) reported that adiponectin was not significantly associated with HRV in male patients with Type 2 diabetes mellitus, although they found that hypoadiponectinemia was associated with sympathetic overactivity. No significant correlations were found between serum adiponectin and LF HRV or HF HRV in another group of patients with Type 2 diabetes (Wakabayashi and Aso, 2004).

Leptin, which is elevated in most obese individuals, stimulates the sympathetic nervous system and increases sympathetic nerve activity to several organs and glands (Eikelis et al., 2003; Haynes, 2000; Mark, 2013; Tang-Christensen et al., 1999). Moreover, the effect of leptin on sympathetic nerve activity is dose-dependent, ranging from 228% ± 63% to 388% ± 171% at 1,000 μg/kg in one study (Haynes et al., 1997). Research has shown that sympathetic activity is associated with the low-frequency range (0.04–0.15 Hz), whereas parasympathetic activity is associated with the higher frequency range (0.15–0.4 Hz) of modulation frequencies of the HRV (Acharya et al., 2006). Our study revealed strong inverse associations between leptin and LF HRV, whereas the association between leptin and HF HRV was not as strong and when stratified by percent body fat, the association between leptin and HF HRV was not statistically significant. Sztajzel et al. (2009) found that the LF component of HRV was lower in both obese and morbidly obese patients, whereas the HF component was lower only in morbidly obese patients, when compared with controls. Leptin also negatively correlated with most HRV indices with the exception of HF. Persons with higher levels of obesity have higher levels of serum leptin, which may explain why stronger associations were observed among officers in our study who had higher levels of overall and abdominal obesity. In our cohort, it appears that sympathetic nervous system function is more likely to be disturbed; however, specifically designed research is necessary to determine whether the association with leptin is differentially associated with sympathetic versus parasympathetic function.

Limitations include the cross-sectional design of this study that limits determination of the chronological sequence of the main variables and inference about causality. Our study also has several strengths. To our knowledge, this is one of very few studies to investigate the association of leptin and adiponectin with HRV. An accredited research laboratory performed standardized analyses of leptin and adiponectin. HRV was assessed by technicians who had expertise in the procedure, and this was done in a standardized manner. HRV measurements are easy to perform, noninvasive, and have good reproducibility, if used under standardized conditions (Kleiger et al., 1991). The sample size was adequate to perform stratified analyses, and many variables were available for assessment as confounders. The results of this study may be generalizable to police officers who work in similar environments and organizational structures like the Buffalo Police Department.

CONCLUSION

In summary, leptin levels were inversely and significantly associated with LF HRV among all officers, and particularly among officers with BMI ± 25 kg/m^2, percent body fat ≥ 25.5%, and higher levels of abdominal adiposity. The prevalence of obesity is increasing among the US population (Ogden et al., 2006). Officers should be educated as to the health implications of obesity, which includes higher leptin levels and reduced HRV leading to a greater risk of CVD morbidity and mortality (Lombardi, 2002). Because of the fact that a multitude of various stressors also activate the sympathetic nervous system (Brydon, 2011), the impli cation of these results is even more important in highly stressed workers such as police officers. These findings could be incorporated and emphasized in health training sessions to police officers who are exposed to a wide variety of conventional as well as unconventional stressors. Studies using prospective designs could reveal the temporal sequence of leptin and HRV. Such studies could also help us to determine whether weight gain leads to decreases in LF HRV, whether reductions in obesity measures lead to improvements in LF HRV, and/or whether decreases in leptin levels lead to improvements in LF HRV. More research is also needed to implement and evaluate interventions to reduce obesity in the workplace.

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TABLE 1

Descriptive results of demographics and other characteristics by gender

Characteristics	All (*n*=388) Mean±SD	Women (*n*=94) Mean±SD	Men (*n*=294) Mean±SD	*P*-value
Age (years; range: 21–70)	41.7±8.0	40.6±6.0	42.1±8.6	0.050
BMI (kg/m^2)	29.2±4.7	26.0±4.8	30.3±4.2	<0.0001
Abdominal height (cm)	20.9±3.5	18.1±3.1	21.7±3.1	<0.0001
Waist circumference (cm)	94.8±14.3	80.5±12.2	99.4±11.6	<0.0001
Body fat (%)	25.5±6.1	30.7±5.9	23.8±5.1	<0.0001
Triglycerides (mg/dl)	137.3±133.9	89.4±138.5	152.3±129.1	<0.0001
Glucose (fasting, mg/dl)	93.0±13.1	86.7±8.3	95.0±13.7	<0.0001
HDL cholesterol (mg/dl)	46.4±14.8	58.5±15.8	42.6±12.3	<0.0001
Physical activity score	21.5±18.3	21.6±17.2	21.4±18.7	0.952
HF HRV (Hz)[a]	144.0 (128.2–161.7)	195.0 (154.0–246.9)	130.6 (114.5–149.1)	0.004
LF HRV (Hz)[a]	204.6 (186.6–224.3)	184.7 (152.4–223.7)	211.4 (190.3–234.8)	0.217
Leptin[a] (pg/ml)	8,196 (7,351–9,139)	11,592 (9,609–13,983)	7,336 (6,451–8,343)	<0.0001
Adiponectin (ng/ml)	13,392±7,321	19,550±8,467	11,422±5,655	<0.0001
	N (%)	*N* (%)	*N* (%)	
Hypertensive	89 (23.1)	17 (18.1)	72 (24.7)	0.188
Diabetic	9 (2.3)	1 (1.1)	8 (2.8)	0.694
Metabolic syndrome	102 (26.5)	8 (8.7)	94 (32.1)	<0.0001
Race/ethnicity				0.024
White	298 (78.2)	67 (71.3)	231 (80.5)	
African American	76 (20.0)	27 (28.7)	49 (17.1)	
Hispanic	7 (1.8)	0 (0)	7 (2.4)	
Education				0.015
≤12 years/GED	40 (10.4)	3 (3.2)	37 (12.7)	
College<4 yrs	208 (54.0)	58 (61.7)	150 (51.6)	
College≥4 yrs	137 (35.6)	33 (35.1)	104 (35.7)	
Police rank				0.173
Patrol officer	267 (70.1)	73 (77.7)	194 (67.6)	
Sergeant/Lieutenant/Captain	58 (15.2)	10 (10.6)	48 (16.7)	
Detective/Executive/Other	56 (14.7)	11 (11.7)	45 (15.7)	
Smoking status				0.036
Current	59 (15.4)	21 (22.8)	38 (13.0)	
Former	95 (24.7)	25 (27.2)	70 (24.0)	
Never	230 (59.9)	46 (50.0)	184 (63.0)	

P-values were obtained from *t*-tests (for continuous variables) and χ^2 tests or Fisher's exact tests (for categorical variables).

[a]Variable was first log-transformed for analysis, and then the results were back-transformed for reporting.

TABLE 2

Associations of selected covariates with the metabolic markers

	Leptin (pg/ml)	Adiponectin (ng/ml)
Age (years)	0.049, 0.334	0.119, 0.019
BMI (kg/m^2)	0.496, <0.0001	−0.328, <0.0001
Abdominal height (cm)	0.448, <0.0001	−0.329, <0.0001
Waist circumference (cm)	0.422, <0.0001	−0.363, <0.0001
Body fat (%)	0.726, <0.0001	0.144, 0.006
Triglycerides (mg/dl)	0.083, 0.104	−0.210, <0.0001
Glucose (fasting, mg/dl)	0.092, 0.072	−0.253, <0.0001
HDL cholesterol (mg/dl)	−0.064, 0.209	0.548, <0.0001
Physical activity score	−0.092, 0.071	0.062, 0.228
Insulin (μU/ml)	0.450, <0.0001	−0.365, <0.0001
Adiponectin (pg/ml)	−0.071, 0.165	na
	Mean (95% CI)	Mean±SD
Hypertension status		
Hypertensive	11,549 (9,235–14,445)	11,824±6,794
Not hypertensive	7,471 (6,610–8,444)	13,859±7,441
P-value[a]	0.001	0.022
Diabetic status		
Diabetic	8,717 (4,264–17,819)	10,179±6,715
Not diabetic	8,260 (7,394–9,228)	13,399±7,255
P-value[a]	0.884	0.188
Metabolic syndrome		
Yes	11,534 (9,354–14,223)	9,530±5,339
No	7,268 (6,409–8,243)	14,701±7,356
P-value[a]	<0.001	<0.0001
Race/ethnicity		
White	7,393 (6,541–8,357)	14,306±7,541
African American	12,576 (9,868–16,027)	10,311±5,850
Hispanic	9,045 (4,068–20,110)	12,109±3,951
P-value[a]	0.001	<0.0001
Education		
≤12 years/GED	9,044 (6,457–12,668)	11,616±6,229
College<4 yrs	8,886 (7,666–10,301)	13,337±7,494
College≥4 yrs	7,294 (6,080–8,751)	14,014±7,377
P-value[b] (from linear contrast)	0.270	0.070
Smoking status		
Current	6,992 (5,294–9,235)	14,871±6,898
Former	8,814 (7,079–10,975)	14,209±8,482

	Leptin (pg/ml)	Adiponectin (ng/ml)
Never	8,304 (7,213–9,561)	12,635±6,880
P-value[a]	0.425	0.049

Leptin was log-transformed for analysis, and then the results were back-transformed for reporting. Results for continuous variables are Pearson's correlation coefficients and *P*-values.

[a] *P*-values are for any difference between the mean values and were obtained from analysis of variance.

[b] *P*-value is for linear trend and was obtained from analysis of variance linear contrasts.

TABLE 3

Mean values and 95% confidence intervals (CIs) of HRV across tertiles of leptin

	Tertiles of leptin			
	First tertile 16–5,781 (*n*=129)	**Second tertile 5,806–13,123 (*n*=130)**	**Third tertile 13,128–91,581 (*n*=129)**	***P*-value**
High frequency				
Model 1	172.7 (141.5–210.9)	148.4 (121.6–181.1)	116.4 (95.3–142.1)	0.087
Model 2	166.4 (137.9–200.7)	147.4 (122.3–177.6)	121.7 (100.8–146.8)	0.144
Model 3	172.5 (142.4–209.0)	149.2 (124.0–179.6)	112.8 (93.2–136.5)	0.028
Low frequency				
Model 1	238.9 (204.4–279.2)	232.2 (198.8–271.3)	154.1 (131.9–180.2)	<0.001
Model 2	233.3 (200.8–271.1)	231.2 (199.2–268.4)	158.5 (136.4–184.2)	<0.001
Model 3	231.9 (198.4–271.2)	231.2 (198.8–269.0)	159.4 (136.4–186.2)	0.001

HF and LF HRV were first log-transformed for analysis, and then the results were back-transformed for reporting. *P*-values were obtained from linear regression models. Model 1: unadjusted; Model 2: adjusted for age; and Model 3: adjusted for age, gender, and race/ethnicity.

TABLE 4

Mean values and 95% confidence intervals (CIs) of HRV across tertiles of leptin, stratified by BMI

	Tertiles of leptin			
	First tertile	**Second tertile**	**Third tertile**	***P*-value**
BMI<25 kg/m^2	16–3,602 (*n*=23)	3,682–5,933 (*n*=24)	6,052–47,043 (*n*=24)	
High frequency				
Model 1	150.0 (97.4–231.2)	221.9 (145.3–338.9)	191.5 (125.4–292.5)	0.500
Model 2	142.4 (93.0–218.0)	227.6 (150.3–344.6)	196.4 (129.7–297.3)	0.521
Model 3	151.2 (94.3–242.6)	224.0 (145.1–345.9)	181.2 (111.6–294.3)	0.918
Low frequency				
Model 1	202.8 (149.3–275.4)	224.2 (166.2–302.5)	166.7 (123.5–224.9)	0.863
Model 2	200.0 (146.8–272.5)	225.7 (167.0–305.0)	167.8 (124.1–226.7)	0.849
Model 3	188.7 (135.3–263.2)	203.5 (149.9–276.2)	193.6 (137.6–272.3)	0.694
BMI≥25 kg/m^2	105–7,021 (*n*=105)	7,189–14,684 (*n*=106)	14,701–91,581 (*n*=106)	
High frequency				
Model 1	160.4 (127.9–201.1)	137.0 (109.4–171.6)	114.5 (91.4–143.4)	0.064
Model 2	152.7 (123.8–188.4)	139.8 (113.5–172.2)	117.7 (95.6–145.1)	0.120
Model 3	159.6 (128.6–198.2)	141.1 (114.5–173.9)	108.8 (87.8–134.9)	0.019
Low frequency				
Model 1	261.2 (218.5–312.4)	227.1 (190.1–271.3)	148.7 (124.4–177.6)	<0.0001
Model 2	252.7 (213.3–299.4)	230.2 (194.5–272.5)	151.5 (128.0–179.3)	<0.0001
Model 3	253.4 (212.1–302.7)	232.0 (195.3–275.5)	151.1 (126.6–180.2)	<0.0001

HF and LF HRV were first log-transformed for analysis, and then the results were back-transformed for reporting. *P*-values were obtained from linear regression models. Model 1: unadjusted; Model 2: adjusted for age; and Model 3: adjusted for age, gender, and race/ethnicity. *P*-values for interaction by BMI in the association between leptin and HF HRV=0.556; leptin and LF HRV=0.002.

TABLE 5

Mean values and 95% confidence intervals (CIs) of HRV across tertiles of leptin, stratified by percent body fat

	Tertiles of leptin			
	First tertile	**Second tertile**	**Third tertile**	***P*-value**
Body fat <25.5%	16–4,024 (*n*=70)	4,035–7,435 (*n*=71)	7,533–91,581 (*n*=70)	
High frequency				
Model 1	188.1 (142.3–248.8)	137.8 (104.4–181.9)	148.2 (112.1–196.0)	0.347
Model 2	182.5 (142.5–233.7)	135.2 (105.8–172.9)	155.7 (121.6–199.4)	0.256
Model 3	180.2 (140.1–231.7)	129.8 (101.2–166.5)	155.3 (120.7–199.8)	0.283
Low frequency				
Model 1	260.8 (210.1–323.9)	218.1 (175.9–270.4)	231.0 (186.1–286.9)	0.418
Model 2	256.6 (209.0–315.0)	215.8 (176.1–264.6)	237.3 (193.3–291.3)	0.366
Model 3	259.6 (210.0–321.0)	215.2 (174.5–265.5)	235.3 (190.3–291.1)	0.348
Body fat ≥ 25.5%	784–12,277 (n=59)	12,396–19,639 (n=59)	20,032–73,657 (n=59)	
High frequency				
Model 1	149.5 (112.2–199.2)	100.1 (75.1–133.4)	147.8 (110.9–196.9)	0.625
Model 2	149.9 (113.1–198.6)	96.5 (72.7–128.0)	152.9 (115.3–202.8)	0.672
Model 3	154.0 (115.7–205.0)	103.1 (77.4–137.3)	140.0 (104.9–187.0)	0.317
Low frequency				
Model 1	216.7 (172.7–272.0)	171.7 (136.8–215.5)	138.2 (110.1–173.5)	<0.001
Model 2	217.2 (173.8–271.3)	166.7 (133.3–208.5)	142.0 (113.6–177.6)	<0.001
Model 3	218.4 (173.4–275.1)	162.2 (128.7–204.3)	146.0 (115.7–184.3)	0.001

HF and LF HRV were first log-transformed, and then the results were back-transformed for reporting. *P*-values were obtained from linear regression models. Model 1: unadjusted; Model 2: adjusted for age; and Model 3: adjusted for age, gender, and race/ethnicity. *P*-value for interaction by percent body fat in the association between leptin and HF HRV=0.748; leptin and LF HRV=0.010.