Published in final edited form as:
Clin Endocrinol (Oxf). 2010 January ; 72(1): 32–37. doi:10.1111/j.1365-2265.2009.03627.x.

Leptinemia and its Association with Stroke and Coronary Heart Disease in the Jackson Heart Study

Jiankang Liu, M.D. Ph.D., **Kenneth R. Butler, Ph.D.**, **Sarah G. Buxbaum, Ph.D.**, **Jung Hye Sung, Sc.D. MPH.**, **Brenda W. Campbell, MPH**, and **Herman A. Taylor, M.D. MPH.**
Jackson Heart Study, Jackson State University, University of Mississippi Medical Center, Jackson, Mississippi 39216-4505, USA

SUMMARY

Background—To examine the association of increased plasma leptin concentration with prevalent stroke and coronary heart disease (CHD) and to examine the genetic contributions of leptin to this association in the Jackson Heart Study cohort.

Methods—A cohort of 5170 participants aged 21-84 years who underwent Exam I during 2000-2004 was analyzed. Odds ratios (OR) of prevalent stroke and CHD were calculated using a logistic regression model adjusted for age, smoking, hypertension and waist circumference (WC). Variance component analysis was used to partition the phenotypic variance of leptin into the polygenic and environmental components.

Results—The prevalence of stroke and CHD was 4.04% and 5.85% in women, and 4.88% and 8.92% in men, respectively. Body mass index (BMI) and WC were highly correlated with leptin both in men and women. In multivariate analysis stratified by sex, leptin was significantly associated with stroke (OR = 1.97, 95% CI 1.21-3.21) in women after adjustment for age, smoking, systolic blood pressure, BMI and WC ($p = 0.0079$). No significant association was observed in men. Heritability of sex-, age-adjusted log-transformed leptin for this cohort was 38.0% and 37.8% after further adjustment for WC and hypertension, respectively. In addition, a sibship effect was also found to be significant and explained 12.2% of the total variance of leptin ($p = 0.007$).

Conclusion—There is a significant association of leptin with stroke in women, which is partly influenced by the genetic factor. The findings suggest that leptinemia is an independent risk factor for stroke in African American women.

Keywords

Leptin; Coronary Heart Disease; Stroke; Jackson Heart Study

Please address all correspondences to: Jiankang Liu, MD., PhD Jackson Heart Study, University of Mississippi Medical Center 350 W. Woodrow Wilson Dr. Jackson, MS 39213-4505 Phone: 601-979-8729; Fax: 601-979-8750 jliu@medicine.umsmed.edu.

Author Contributions: Dr. Liu had full access to all of the data in the study and takes responsibility for integrity of the data and accuracy of data analysis.
Study Concept and Design: Drs. Liu, Taylor, Butler and Buxbaum.
Acquisition of data: Drs. Taylor, Liu, Sung and Buxbaum.
Analysis and Interpretation of data: Drs. Liu, Taylor, Butler, Sung and Buxbaum.
Drafting of the manuscript: Drs. Liu, Taylor, Butler Buxbaum, and Campbell.
Critical revisions of the manuscript for important intellectual content: Drs. Taylor, Liu Butler and Campbell.
Statistical analysis: Drs. Liu, Sung and Buxbaum.
Obtained funding: Dr. Taylor

Disclosure: The authors declared no conflict of interest.

INTRODUCTION

Leptin, a circulating peptide hormone produced by adipocytes that regulates body weight by decreasing appetite and increasing energy expenditure, may mediate several cardiovascular manifestations through metabolic and neuroendocrine pathways on blood pressure.1 In experimental studies, leptin was found to activate sympathetic nervous system activity and to alter kidney function, leading to elevation of blood pressure or hypertension.2,3 In human studies, leptin was shown to be an important risk factor for cardiovascular disease (CVD) associated with obesity. 1,4 Consistent with this notion are several large population-based studies suggesting strong positive association between increased plasma leptin levels and vascular complications, including hypertension, diabetes, coronary heart disease and stroke, in Mauritian men of African or Indian , Japanese men and European populations.4-7 Results from HERITAGE family study and Finnish Twin study indicated this positive association was partly attributable to a strong familial effect on variation in plasma leptin levels.8,9 Although obesity and increased plasma leptin concentration have been correlated with elevated blood pressure,2,3 relatively few studies have examined the relation of leptin to CHD and stroke, especially in the African American population. Recent data analyses from the Jackson Heart Study (JHS) 2000-2004, a population-based CVD study in an African American cohort, demonstrated higher prevalence of hypertension, metabolic syndrome, coronary heart disease (CHD) and stroke.10,11 In addition, increased plasma leptin concentration has been reported to be favorably associated with vascular function only in obese Caucasians, not in obese Africans.12 However, the role of leptin in the pathogenesis of obesity-related CHD and stroke in the African American population remains undefined.

Despite the growing literatures showing the association between obesity and leptin as well as between leptin and hypertension, the etiological mechanisms in the relationships of leptin to CHD and stroke in African Americans are still unclear. The aims of this study were to assess the cross-sectional relationships of leptin to CHD and stroke in the JHS cohort, and to determine whether the variability of leptin is due to shared genetic or common environmental factors.

METHODS

Study Sample

The JHS is a prospective population-based investigation of the predictors and outcomes of CVD and related disorders among African-Americans. The original design and sampling plan for the JHS has been previously described. 13 Briefly, the JHS cohort was assessed during the first clinic exam (September 2000 to March 2004) and comprised 5301 participants in total, consisting of 5035 adults aged 35-84 years, and an additional 251 participants aged 21-34 years and 15 subjects aged > 85 years. The latter group entered the study to increase the power of JHS Family component. The final age range was 21 to 94 years.14,15 We have excluded participants who did not have the plasma leptin measurement from this analysis. The final sample size of this study was 5,170. The study was approved by the Institutional Review Board of the participating institutions: the University of Mississippi Medical Center, Jackson State University and Tougaloo College. All of the participants provided informed consent.

Risk Factors and Covariate Assessment

The standard examination included a home interview and clinic visit, a physical examination and laboratory tests. Sociodemographic, lifestyle/risk factors (including extensive dietary and physical activity information), psychological parameters and history of health care

provider-diagnosed cardiovascular conditions as well as other data were obtained through standard procedures using questionnaires.

Body mass index (BMI), defined as weight (in kilograms) divided by the square of height (in meters), was measured at the baseline examination. Two measures of waist circumference (WC) were taken at the level of the umbilicus on each participant and averaged to determine baseline WC. Fasting blood samples were collected according to standardized procedures and the assessments of plasma glucose, lipids and leptin were processed at the Central Laboratory (University of Minnesota) as described in previous publications.14,15 Leptin was analyzed with Human Leptin RIA kit (LINCO Research, St. Charles, MI) and the acceptable coefficients of variation is 10%. Low-density lipoprotein (LDL) was calculated according to the following formula: LDL = total cholesterol − (triglycerides/5) - HDL. If the triglyceride level was >10.36 mmol/L, LDL was not calculated and reported as a missing value. The average of two sitting blood pressure, measured at 5-minute intervals, was used for analysis. Subjects were considered current smokers if they smoked at the time of the interview. The alcohol status was YES if they drank in past 12 month. In addition, ATP III definition was used to define the presence of metabolic syndrome. The presence of type 2 diabetes mellitus (diabetes) was determined by a measured fasting glucose > 6.93 mmol/L, a history of physician-diagnosed diabetes or the use of hypoglycemic medications (self-reported or actual). Subjects were considered to be hypertensive if they were taking antihypertensive medications (actual or self-reported), self-reported a diagnosis of hypertension, and/or if their systolic pressures were ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg.

Definition of CHD and Stroke

Prevalent CHD was defined as evidence of a previous myocardial infarction by ECG based on Minnesota Code criteria (Codes 1.1 and 1.2 plus 4.1-4.2, or 5.1-5.2) or history of physician-diagnosed myocardial infarction, percutaneous coronary intervention or coronary bypass surgery. The definition of stroke was based on the history of stroke (by personal history, stroke signs and symptoms ascertained by standardized questionnaires), transient ischemic attack or carotid endarterectomy and/or angioplasty. Details of these procedures have been described previously.16

Statistical Analysis

Due to differences in the distribution of plasma leptin concentration in our cohort, all analyses were sex-specific. Within each sex, leptin and insulin were normalized by logarithmic transformation and the central tendency and spread represented by the median and interquartile ranges. For each individual risk factor, the student unpaired t-test was carried out for the significance of the difference between men and women. The relationships between ***log-leptin*** and individual cardiovascular risk factors including BMI, WC, triglyceride, LDL-C, HDL-C, fasting plasma glucose, blood pressure were assessed by calculating partial correlation coefficients adjusted for age. ***A logistic linear regression model was used*** to assess the association of either CHD or stroke as dependent variables with ***log-leptin***, BMI, WC, fasting plasma glucose, blood pressure, smoking and hypertension as independent variables. ***Log-leptin*** was included in the models as a dichotomous variable (high leptin defined as > 3rd quartile of cohort distribution vs. ***not high leptin*** as < 3rd quartile). The analyses excluded persons with missing values for leptin. A 95% confidence interval (95% CI) for odd ratio that did not include 1 ***($p < 0.05$)*** was considered to indicate statistical significance. All analyses were performed using the SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Heritability Analysis

A variance components analysis was used to partition the phenotypic variance of leptin into additive polygenic and environmental variance components. This tested whether correlations among family members for leptin might solely be environmental or genetic. In this way, heritability for leptin was estimated and adjusted for age, sex, smoking, WC and hypertension to ascertain evidence of genetic control of leptin. The ASSOC program in S.A.G.E. v.5.4.0 was used to estimate the heritability (h^2) of leptin, the ratio of the polygenic variance to the total variance. A spousal effect (an effect common to the parents of a child or children), a nuclear family effect (an effect common to all members of the same nuclear family) and a sibship effect (an effect that full siblings share with each other, thus allowing for dominance variance and common sibling environmental variance) were also considered in the analysis.

RESULTS

The sex-specific descriptive statistics of BMI, WC, plasma leptin and glucose, lipid profiles, smoking/drinking status, hypertension, diabetes and metabolic syndrome were demonstrated in Table 1 according to the presence or absence of CHD and stroke. Women had significantly higher levels of plasma leptin compared to men (p=0.0001). With cardiovascular outcomes, women also had higher levels of HDL-C, fasting insulin but lower diastolic blood pressure than men. No significance was found in plasma glucose, TG, LDL-C and systolic blood pressure between men and women. However, it is noteworthy that the prevalence of hypertension, diabetes and metabolic syndrome in women was higher than in men. To illustrate the relationship between leptin and the risk factors, age-adjusted partial correlations between leptin and BMI, WC, glucose, triglyceride, LDL-C, HDL-C, systolic and diastolic blood pressure were presented in Table 2. As expected, ***log-leptin*** was correlated positively with cardiometabolic risk factors including BMI, WC, fasting insulin, glucose and triglyceride, but negatively with HDL-C levels both in men and women. A correlation of ***log-leptin*** with systolic and diastolic blood pressure was only observed in men.

In a logistic regression analysis, high leptin level was significantly associated with stroke in women. After adjustment for age, smoking, BMI, WC and HTN, the association still remained significant. No significant association was observed between leptin and CHD both in men and women (Table 3).

Heritability was used to summarize overall familiarity, the extent of the effect of familial factors on variation of leptin. The heritability estimate for leptin explained 38% of total familial variance after adjusting for age and sex. This analysis was repeated and further adjusted for WC and hypertension. The heritability of leptin was slightly changed, which explained 37.8% of total familial variance (p value < 0.0001). In addition to the polygenic component, an extra sibship variance component was also found to be significant, explaining 12.2% of the total variance of leptin (p = 0.007) as a cohort effect. No significance of nuclear family or spouse effect was found in this analysis.

DISCUSSION

This study examined the association of leptin with CHD and stroke in a population-based cohort of African American men and women. The principle findings were that leptin was a significant cardiovascular risk factor for stroke in African American women independent of traditional cardiovascular risk factors. In addition, leptin was demonstrated to be a highly heritable factor, resulting from the effects of polygenic and sibship components in the JHS cohort.

CHD and stroke are the leading causes of the death and disability among adults in the US.17 Even though the cerebral and myocardial vasculatures are different,18 the occurrence of CHD and stroke are related to common traditional cardiovascular risk factors such as smoking, obesity, hypertension and diabetes. Therefore, it could be expected that the potential mechanisms that stimulate the development of stroke and CHD would be similar for these two diseases. However, studies demonstrated that changes and levels of rates in these two diseases were not similar for their patterns in the populations, suggesting the fundamental elements that determine the diseases may be more complex.19,20 In addition to the supportive evidence that higher incidence of CHD and stroke is correlated with the higher prevalence of obesity,21 the mechanism by which obesity results in higher incidence of stroke and CHD has not been fully explained.

Generally, women have higher fat percentages and therefore the increased leptin secreted may contribute to the development of CVD via its effects on blood pressure, insulin sensitivity, abnormal homeostasis and impaired fibrinolysis, which are features of insulin resistance and obesity.1,4,22 Gender-specific associations of leptin with diabetes, CVD and stroke had been reported in several epidemiological studies 5, 22–27 However, results from prior studies were slightly not consistent due to the differences in sample size, geographical location and ethnic groups. The current analysis from the JHS, a largest population-based CVD study in African American cohort, demonstrated that leptin is a risk factor for stroke in African American women, independent of age, smoking, obesity status and hypertension. This sex-specific difference was also observed in recent JHS results in the prevalence of abdominal obesity, hypertension and metabolic syndrome that significantly related to the sex-specific prevalence of CHD and stroke.11 Several possible mechanisms proposed that could contribute to a sex-specific difference in association between leptin and CVD, including the difference in leptin signaling pathway in the central nervous system,28 the effect of sex hormones29 and perhaps most importantly, a sex-specific relationship between leptin, insulin resistance and the resulting hyperinsulinemia in the development of CVD.27

Approximate heritability estimates of 38% in the families of the JHS cohort were consistent with a previous report in the African American population by another group.30 This high heritability estimate was significant for leptin even after adjustments for age, sex, WC and hypertension, suggesting that the association between leptin and stroke is partly explained by the genetic influence. In addition to the polygenic component, a sibship effect was also found to be significant and might be understood as a cohort effect. The results indicated that leptin at any ages, gender and obesity levels were substantially determined by genetic background, which link leptin to CVD in this cohort.

There are several strengths of the present study. First, standardized laboratory and the analytical protocols were utilized. Second, it is a well-characterized cross-sectional study of a large population-based cohort of African Americans. This provided an opportunity to characterize the contribution of leptin as a contemporaneous factor as well as traditional risk factors of CHD and stroke. Furthermore, this study demonstrated the leptin was a possible cardiovascular risk marker of CVD in African Americans. It should be noted that the mean plasma leptin concentration was much higher than previously reported from NHANES III data, 6 especially among women. This is partly due to the fact that our study sample has a higher prevalence of obesity.11 But to some extent, the genetic factors exert their impact on the association between increased plasma leptin concentration and CHD or stroke in this cohort.

The principal limitation of this analysis is the use of cross-sectional data, necessitated by the use of the initial data from a new cohort. Thus, causal pathways underlying the observed relationships cannot be inferred. Also, the prevalence of stroke in the present analysis is

mainly based on self-report that may reduce its actual prevalence and are subject to memory recall bias, potentially underestimating the prevalence of the diseases. Finally, although an association between leptin and stroke was not found to be statistically significant in men, ORs were similar to the women (1.97 for women vs. 1.70 for men). This is likely due to a lack of study power because sample size for women (n = 2928) was much larger than the men (n = 1643). This limitation may weaken the opportunity to find any statistically significant association in men.

In conclusion, this study demonstrated leptin was a statistically significant risk factor of stroke in women and a potential clinically significant risk factor of stroke in men independent of traditional CVD risk factors. The relationship between leptin and stroke was extensively influenced by heritable factors. The findings coming out from this study may contribute to more wide-spread clinical application of leptin evaluation as a risk for CVD. Future studies are warranted to elucidate the relationship of leptin and cardiovascular disease outcomes in African Americans. As these new studies clarify leptin's role in CVD, more powerful genome wide association scans for specific genes and gene variants can be examined and evaluated in tandem.

Acknowledgments

The authors thank the staff, interns and participants in Jackson Heart Study for their long-term commitment and important contributions to the study. Part of the results in this paper was obtained by using the program package S.A.G.E., which is supported by a U.S. Public Health Service Resource Grant (RR03655) from the National Center for Research Resources. We also thank Boshen Liu, a student of Lehigh University, for his efforts on an early draft of manuscript and reference reviews.

Funding / Support: Funding for Dr. Taylor was provided under contracts N01-HC-95170, N01-HC-95171 and N01-C-95172 from the National Heart, Lung and Blood Institute and the National Center on Minority Health and Health Disparities.

Reference List

(1). Patel SB, Reams GP, Spear RM, Freeman RH, Villarreal D. Leptin: linking obesity, the metabolic syndrome, and cardiovascular disease. Current Hypertension Reports. 2008; 10:131–7. [PubMed: 18474180]

(2). Hall JE, Jones DW, Kuo JJ, da SA, Tallam LS, Liu J. Impact of the obesity epidemic on hypertension and renal disease. Current Hypertension Reports. 2003; 5:386–92. [PubMed: 12948431]

(3). Hall JE, Crook ED, Jones DW, Wofford MR, Dubbert PM. Mechanisms of obesity-associated cardiovascular and renal disease. American Journal of the Medical Science. 2002; 324:127–37.

(4). Wannamethee SG, Tchernova J, Whincup P, Lowe GD, Kelly A, Rumley A, Wallace AM, Sattar N. Plasma leptin: associations with metabolic, inflammatory and haemostatic risk factors for cardiovascular disease. Atherosclerosis. 2007; 191:418–26. [PubMed: 16712853]

(5). Soderberg S, Stegmayr B, Stenlund H, Sjostrom LG, Agren A, Johansson L, Weinehall L, Olsson T. Leptin, but not adiponectin, predicts stroke in males. Journal of Internal Medicine. 2004; 256:128–36. [PubMed: 15257725]

(6). Sierra-Johnson J, Romero-Corral A, Lopez-Jimenez F, Gami AS, Kuniyoshi FH Sert, Wolk R, Somers VK. Relation of increased leptin concentrations to history of myocardial infarction and stroke in the United States population. American Journal of Cardiology. 2007; 100:234–9. [PubMed: 17631076]

(7). McNeely MJ, Boyko EJ, Weigle DS, Shofer JB, Chessler SD, Leonnetti DL, Fujimoto WY. Association between baseline plasma leptin levels and subsequent development of diabetes in Japanese Americans. Diabetes Care. 1999; 22:65–70. [PubMed: 10333905]

(8). Rice T, Chagnon YC, Borecki IB, Pérusse L, Collier G, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Familial resemblance for plasma leptin: sample homogeneity across adiposity and ethnic groups. Obesity Research. 2002; 10:351–60. [PubMed: 12006634]

(9). Kaprio J, Eriksson J, Lehtovirta M, Koskenvuo M, Tuomilehto J. Heritability of leptin levels and the shared genetic effects on body mass index and leptin in adult Finnish twins. International Journal of Obesity and Related Metabolic Disorders. 2001; 25:132–7. [PubMed: 11244469]

(10). Wyatt SB, Akylbekova EL, Wofford MR, Coady SA, Walker ER, Andrew ME, Keahey WJ, Taylor HA, Jones DW. Prevalence, awareness, treatment, and control of hypertension in the Jackson Heart Study. Hypertension. 2008; 51:650–6. [PubMed: 18268140]

(11). Taylor H, Liu J, Wilson G, Golden SH, Crook E, Brunson CD, Steffes M, Johnson WD, Sung JH. Distinct component profiles and high risk among African Americans with metabolic syndrome: the Jackson Heart Study 26. Diabetes Care. 2008; 31:1248–53. [PubMed: 18332154]

(12). Schutte R, Huisman HW, Schutte AE, Malan NT. Leptin is favourably associated with vascular function in obese Caucasians, but not in obese Africans. Journal of Human Hypertension. 2005; 19:933–9. [PubMed: 16094408]

(13). Taylor HA Jr. Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, Nelson C, Wyatt SB. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. Ethnicity & Disease. 2005; 15:S6–17.

(14). Wilson JG, Rotimi CN, Ekunwe L, Royal CD, Crump ME, Wyatt SB, Steffes MW, Adeyemo A, Zhou J, Taylor HA Jr. Jaquish C. Study design for genetic analysis in the Jackson Heart Study. Ethnicity & Disease. 2005; 15:S6–37.

(15). Fuqua SR, Wyatt SB, Andrew ME, Sarpong DF, Henderson FR, Cunningham MF, Taylor HA Jr. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. Ethnicity & Disease. 2005; 15:S6–29. [PubMed: 16317982]

(16). Keku E, Rosamond W, Taylor HA Jr. Garrison R, Wyatt SB, Richard M, Jenkins B, Reeves L, Sarpong D. Cardiovascular disease event classification in the Jackson Heart Study: methods and procedures. Ethnicity & Disease. 2005; 15:S6–70. [PubMed: 16317987]

(17). Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008; 117:e25–146. [PubMed: 18086926]

(18). Granstam SO, Granstam E, Fellström B, Lind L. Regional haemodynamic differences between normotensive and spontaneously hypertensive rats--a microsphere study. Physiological Research. 1998; 47:9–15. [PubMed: 9708695]

(19). Reed DM. The paradox of high risk of stroke in populations with low risk of coronary heart disease. American Journal of Epidemiology. 1990; 131:579–88. [PubMed: 2316492]

(20). Truelsen T, Mahonen M, Tolonen H, Asplund K, Bonita R, Vanuzzo D. Trends in stroke and coronary heart disease in the WHO MONICA Project. Stroke. 2003; 34:1346–52. [PubMed: 12738889]

(21). Walker SP, Rimm EB, Ascherio A, Kawachi I, Stampfer MJ, Willett WC. Body size and fat distribution as predictors of stroke among US men. American Journal of Epidemiology. 1996; 144:1143–50. [PubMed: 8956626]

(22). Sheu WH, Lee WJ, Chen YT. High plasma leptin concentrations in hypertensive men but not in hypertensive women. Journal of Hypertension. 1999; 17:1289–95. [PubMed: 10489106]

(23). Söderberg S, Zimmet P, Tuomilehto J, Chitson P, Gareeboo H, Alberti KG, Shaw JE. Leptin predicts the development of diabetes in Mauritian men, but not women: a population-based study. International Journal of Obesity. 2007; 31:1126–33. [PubMed: 17325688]

(24). Takizawa H, Ura N, Saitoh S, Wang L, Higashiura K, Takagi S, Takada M, Togashi N, Nakano M, Hayashi Y, Shimamoto K. Gender difference in the relationships among hyperleptinemia, hyperinsulinemia, and hypertension. Clinical and Experimental Hypertension. 2001; 23:357–68. [PubMed: 11349826]

(25). Lawlor DA, Smith GD, Kelly A, Sattar N, Ebrahim S. Leptin and coronary heart disease risk: prospective case control study of British women. Obesity. 2007; 15:1694–701. [PubMed: 17636087]

(26). Söderberg S, Colquhoun D, Keech A, Yallop J, Barnes EH, Pollicino C, Simes J, Tonkin AM, Nestel P. LIPID Study Investigators. Leptin, but not adiponectin, is a predictor of recurrent cardiovascular events in men: results from the LIPID study. International Journal of Obesity. 2009; 33:123–30. [PubMed: 19050671]

(27). Flanagan DE, Vaile JC, Petley GW, Phillips DI, Godsland IF, Owens P, Moore VM, Cockington RA, Robinson JS. Gender differences in the relationship between leptin, insulin resistance and the autonomic nervous system. Regulatory Peptides. 2007; 140:37–42. [PubMed: 17187873]

(28). Kushi A, Sasai H, Koizumi H, Takeda N, Yokoyama M, Nakamura M. Obesity and mild hyperinsulinemia found in neuropeptide Y-Y1 receptor-deficient mice. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95:15659–64. [PubMed: 9861026]

(29). Martin LJ, Mahaney MC, Almasy L, MacCluer JW, Blangero J, Jaquish CE, Comuzzie AG. Leptin's sexual dimorphism results from genotype by sex interactions mediated by testosterone. Obesity Research. 2002; 10:14–21. [PubMed: 11786597]

(30). Rotimi C, Luke A, Li Z, Compton J, Bowsher R, Cooper R. Heritability of plasma leptin in a population sample of African-American families. Genetic Epidemiology. 1997; 14:255–63. [PubMed: 9181355]

Table 1

Sex-Specific Descriptive Characteristics of the JHS Participants with or without Stroke/Coronary Heart Disease[#]

	No conditions		Stroke		CHD	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**
Participants (n)	2928	1643	132	93	191	170
Prevalence (%)	0	0	4.04	4.88	5.85	8.92 ‡
BMI (kg/m^2)	33±8	30±6 ‡	33±7	29±6 ‡	33±7	30±6 ‡
W C (cm)	100±17	101±15 ‡	105±15	103±14	101±16	103±14
Leptin (ng/ml)*	33 (22,47)	8 (5, 14) ‡	39 (26, 54)	9 (5, 13) ‡	30 (21, 46)	10(6,17) ‡
LDL-C (mmol/L)	3.27±0.94	3.35±0.95 #	3.14±0.90	3.25±0.97	3.10±0.99	3.10±0.90
HDL-C (mmol/L)	1.43±0.38	1.19±0.32 ‡	1.36±0.37	1.23±0.33 †	1.38±0.45	1.78±0.39 ‡
TG (mmol/L)	1.13±0.74	1.30±1.05 †	1.25±0.73	1.26±0.75	1.29±0.63	1.30±0.91
Glucose (mmol/L)	5.49± 1.79	5.50±1.67 ‡	6.30±2.66	6.33±3.19	5.99±1.95	6.23±2.93
Insulin (pmol/L)*	111(76, 152)	90 (69, 138) †	131 (90, 215)	97 (69, 160) †	125 (90, 215)	104 (69, 174)
SBP (mmHg)	126±19	127±17 †	133±19	132±20	132±19	130±21
DBP(mmHg)	77±10	82±11 ‡	75±13	79±10 †	74±11	80±12 ‡
HTN (%)	62	56 ‡	92	89	92	87
HTN Med (%)	52	38 ‡	83	73	83	72 ‡
Lipid Lowering Med (%)	11.4	9.8	31	33	39	39
DM (%)	18	14 ‡	36	38	37	31
MetS (%)	42	31 ‡	65	44 ‡	62	47 ‡
Current Smoker (%)	10	17 ‡	12	24 ‡	17	21 ‡
Alcohol Use (%)	40	61 ‡	20	37 †	78	46 ‡

BMI indicates body mass index; WC, waist circumference; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; MetS, metabolic syndrome; HTN, hypertension; Med, medication.

[#]Data are presented as mean ± SD or as percentage when appropriate.

‡ $p < 0.0001$;

# $p < 0.001$;

† $p < 0.05$ for comparison between men and women in each group.

* Median (25^{th}, 75^{th} percentile)

Table 2

Age-Adjusted Partial Correlation of log-Leptin to Individual Cardiovascular Risk Factors

Variables	Men (n=1906)		Women (n=3264)	
	r	p value	r	p value
BMI	0.73	0.0001	0.65	0.0001
W C	0.77	0.0001	0.61	0.0001
LDL-C	0.10	0.0001	0.06	0.0009
HDL-C	−0.27	0.0001	−0.10	0.0001
TG	0.25	0.0001	0.10	0.0001
Glucose	0.17	0.0001	0.08	0.0001
Log insulin	0.59	0.0001	0.42	0.0001
SBP	0.11	0.0001	0.01	0.45
DBP	0.08	0.0005	0.008	0.66

BMI indicates body mass index; WC, waist circumference; LDL-C , low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3

Association of Stroke or Coronary Heart Disease with Leptin Adjusted for Other CVD Risk Factors in Men or Women*

	Models and Adjustment	Stroke	CHD
		OR (95% CI)	OR (95% CI)
Women	High Leptin	1.68 (1.18-2.38)**	0.92 (0.68-1.25)
	Adjusted for age	1.91 (1.34-2.72)***	1.05 (0.77-1.43)
	Adjusted for SBP	1.78 (1.23-2.58)**	0.83 (0.61-1.13)
	Adjusted for Age, SBP, Smoking, Glucose, BMI, WC	1.97 (1.21-3.21)**	0.96 (0.66-1.39)
Men			
	High Leptin	1.98 (0.69-5.67)	1.00 (0.36-2.85)
	Adjusted for age	1.66 (0.65-4.91)	0.90 (0.31-2.62)
	Adjusted for SBP	1.59 (0.55-4.59)	0.80 (0.81-2.30)
	Adjusted for Age, SBP, Smoking, Glucose, BMI, WC	1.70 (0.51-5.68)	0.72 (0.23-2.23)

BMI indicates body mass index; WC, waist circumference; SBP, systolic blood pressure.

* OR (odds ratio) and its 95% confident interval are calculated for stroke and CHD.

*** $p < 0.0001$;

** $p < 0.001$.