Association of low leptin with cardiovascular events and mortality in patients with stable coronary artery disease: The Heart and Soul Study

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ABSTRACT

Objective: Leptin is an adipokine with both protective and harmful effects on the cardiovascular (CV) system. Prior studies evaluating the association between leptin and CV outcomes have yielded conflicting results. Thus, we sought to investigate the relationship between leptin and CV events and mortality in patients with chronic stable coronary artery disease (CAD).

Methods: We performed a prospective cohort study of 981 outpatients with stable CAD. Leptin levels were measured in fasting venous samples at baseline. We used proportional hazards models to evaluate the association of baseline leptin with subsequent CV events (myocardial infarction, stroke, transient ischemic attack) and death.

Results: During a mean follow-up of 6.2 ± 2.1 years, there were 304 deaths, 112 myocardial infarctions, and 52 strokes/TIAs. In models adjusted for age, sex, and race, low leptin was associated with a 30% increased risk of the combined outcome (HR 1.30, CI 1.05–1.59, $p = 0.01$). After further adjustment for obesity, traditional CV risk factors and biomarkers, low leptin remained associated with a 37% increased risk of events (HR 1.37, CI 1.06–1.76, $p = 0.02$).

Conclusions: Low leptin is associated with increased CV events and mortality in patients with stable coronary artery disease. This association is independent of known factors affecting leptin levels, including gender and obesity.

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1. Introduction

Discovered in 1994, leptin is the product of the obesity (*ob*) gene and is a 16-kDa hormone with pleiotropic actions in multiple organ systems [1]. There is increasing interest in the potential role of leptin in the cardiovascular (CV) system, as accumulating evidence suggests that leptin is involved in insulin sensitivity, angiogenesis, vascular and endothelial function, and myocyte proliferation [2]. Thus, examination of leptin signaling may provide insight into the complex relationship between obesity and CV disease.

Currently, the literature is replete with contradictory results on leptin-related effects on the CV system. In animal and *in vitro* models, leptin increases oxidative stress in endothelial cells [3], which promotes atherogenesis. In contrast, leptin also induces nitric oxide production, which is anti-atherogenic [4]. Leptin has been implicated in increased platelet reactivity and thrombosis [5]. Yet exogenous leptin during early reperfusion reduces infarct size [6].

Human studies on leptin and coronary artery disease (CAD) have also reported conflicting results [7]. In populations without CAD, a few studies have shown leptin to be associated with increased risk of incident CAD [8–10], while others found no association [11–14]. Others have reported a protective association of leptin with decreased CV mortality in populations with diabetes [15] and chronic kidney disease [16]. However, prospective data on leptin and prognosis in established CAD are sparse. In one study of a heterogeneous population ranging from acute coronary syndromes to minimal angiographic stenoses, higher leptin was associated with an increased risk of cardiac death, myocardial infarction, stroke, or revascularization [17]. We investigated the relationship between leptin and CV events and mortality in a prospective cohort study of 981 patients with chronic stable CAD.

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2. Methods

2.1. Participants

The Heart and Soul Study is a prospective cohort study investigating the effect of psychosocial factors on prognosis in stable CAD [18]. Participants were recruited from clinics at the San Francisco Veterans Affairs (VA) Medical Center, the Palo Alto VA Health Care System, the University of California San Francisco Medical Center, and the San Francisco Community Health Network. The enrollment process has been previously described [19]. Subjects were eligible if they met one of the following criteria: (1) history of myocardial infarction (MI), (2) history of coronary revascularization, (3) ≥50% angiographic stenosis in at least one coronary artery, (4) exercise-induced ischemia by treadmill electrocardiogram or nuclear perfusion imaging. Exclusion criteria were: (1) history of MI within the past six months, (2) inability to walk one block, (3) intention to move out of the local area within three years. The protocol was approved by the appropriate institutional review boards, and all participants provided written informed consent.

Between September 2000 and December 2002, 1024 participants enrolled in the study. Of these, 549 (54%) had a history of myocardial infarction, 237 (23%) had a history of revascularization, and 238 (23%) had CAD documented by a physician based on angiogram or stress test. All participants completed a baseline study visit that included an interview, questionnaire, 12-h fasting blood draw, and exercise treadmill test with baseline and stress echocardiograms. Serum was stored at −70 °C. We excluded 39 subjects who did not have sera available for leptin measurement and four subjects for whom no follow up data were available, leaving 981 subjects for this analysis.

2.2. Leptin assay

Leptin was measured by immunoassay of thawed fasting serum samples by the Milliplex Map Kit (Millipore, St. Charles, MO). The inter-assay coefficient of variation was 9.9–11.9%, and only 3% of replicate pairs had greater than 20% coefficient of variation. The laboratory technicians were blinded to patient characteristics and outcomes.

2.3. Biomarkers

Creatinine, HDL- and LDL-cholesterol, fasting glucose, hemoglobin A1c, triglycerides, and high-sensitivity C-reactive protein (CRP) were measured in a clinical laboratory setting. Insulin and adiponectin levels were measured with the Linco Multiplex immunoassay (Millipore, St. Charles, MO).

2.4. Other measurements

Age, sex, race, smoking and alcohol use, physical activity, and medical history were collected by self-report questionnaire. Smoking was defined as current tobacco use. Diabetes was defined as self-report of diabetes, fasting glucose ≥126 mg/dL, or taking diabetic medications. Physical activity level was assessed by questionnaire with a 5-point scale, and then dichotomized. Participants were instructed to bring their medication bottles to the study appointment, and study personnel categorized current medications using Epocrates Rx (San Mateo, CA). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured midway between the lower rib margin and the iliac crest, to the nearest 0.1 cm. Resting echocardiography was performed in all subjects using an Acuson Sequoia Ultrasound System (Siemens, Mountain View, CA) with a 3.5-MHz transducer. Left ventricular ejection fraction (LVEF) was calculated

as (end diastolic volume − end systolic volume)/end diastolic volume.

2.5. Outcome

The outcome variable was time to myocardial infarction, stroke, transient ischemic attack or death. We also analyzed all-cause mortality and nonfatal CV events separately. Annual telephone interviews with participants or their proxies were conducted regarding recent emergency room visits, hospitalizations, or death. For any reported event, two independent and blinded adjudicators reviewed medical records, electrocardiograms, death certificates, and coroner's reports. If the adjudicators agreed on the outcome classification, their classification was binding. If they disagreed, a third blinded adjudicator reviewed the event and determined the outcome classification. Nonfatal myocardial infarction was defined using standard criteria [20]. Stroke was defined as a new neurological deficit not known to be secondary to brain trauma, tumor, infection, or other cause. Transient ischemic attack (TIA) was defined as a focal neurological deficit (in the absence of head trauma) lasting more than 30 s and no longer than 24 h, with rapid evolution of symptoms to maximum deficit in less than 5 min and subsequent complete resolution. Death was determined by death certificates and coroner's reports.

2.6. Statistical analysis

Because there is no standard cut-off for normal leptin levels, and since leptin levels are higher in women, we used sex-specific median values to dichotomize leptin. Differences in baseline characteristics of participants were compared by leptin levels using Student's T-test for normally distributed variables, the Mann–Whitney test for non-normally distributed continuous variables, and chi-squared test for dichotomous variables. Log rank tests were used to determine whether differences between Kaplan–Meier curves were statistically significant.

We estimated the independent associations of leptin with combined events (MI, stroke/TIA, death), total mortality, and nonfatal CV events using Cox proportional hazards models. We considered leptin both as continuous and split at the sex-specific medians. For multivariable models, potential covariates were chosen a priori based on prior studies, biologic plausibility, or association with leptin ($p \leq 0.1$) in bivariate analysis. Age, white race, and sex were included in the models for face validity. Participants were censored at date of death or last contact. We used Wald tests to assess modification of the effects of leptin by BMI, waist circumference, sex, diabetes, and adiponectin in age-adjusted models. Standard BMI categories were used in the stratified analyses. Linear regression and Wald test for heterogeneity were used to evaluate the association between BMI and leptin.

In model checking, we assessed log–linearity using restricted cubic splines, which were retained for fasting glucose, creatinine, and adiponectin in the final models. Also to improve linearity, leptin and CRP were natural-log transformed. We verified the proportional hazards assumption using log-minus-log survival plots, Cox–KM plots, and by checking for secular patterns in scaled Schoenfeld residuals. We assessed for collinearity between predictors by pairwise correlations. Statistical analysis was performed using STATA IC, version 11 (Stata Corp, College Station, TX).

3. Results

The 981 subjects included in the analysis had a median leptin level of 8.1 ng/mL (interquartile range, 3.8–16.6 ng/mL). There were no statistically significant differences in baseline leptin levels or outcomes between included ($n = 981$) and excluded ($n = 43$)

Table 1
Baseline characteristics of participants by low versus high leptin.

	Leptin category		p value[*]
	Low (below sex-specific median value)	High (above sex-specific median value)	
Range for men (ng/mL)	0.04–6.76	6.77–4615	
Range for women (ng/mL)	0.3–17.5	17.6–473	
Number of subjects	491	490	
Demographic variables			
Age (years)	67 ± 12	67 ± 10	0.55
Male	400 (81%)	400 (82%)	0.95
White	300 (61%)	291 (59%)	0.56
Medical history			
Hypertension	322 (66%)	369 (75%)	0.001
Prior myocardial infarction	266 (54%)	259 (53%)	0.76
Congestive heart failure	75 (15%)	98 (20%)	0.06
Prior stroke	63 (13%)	75 (15%)	0.25
Diabetes	114 (23%)	145 (30%)	0.02
Current smoker	114 (23%)	79 (16%)	0.005
Alcohol use	151 (31%)	133 (27%)	0.18
Physically inactive	235 (48%)	273 (56%)	0.01
Medication use			
Aspirin	369 (75%)	390 (80%)	0.10
ACE inhibitor or ARB[a]	227 (46%)	278 (57%)	0.001
Beta blocker	277 (56%)	286 (58%)	0.54
Statin	296 (60%)	335 (68%)	0.008
Loop or thiazade diuretic	117 (24%)	174 (36%)	<0.001
Measurements			
Systolic blood pressure (mmHg)	133 ± 22	133 ± 20	0.98
Diastolic blood pressure (mmHg)	75 ± 11	74 ± 11	0.52
Body mass index (kg/m^2)	26 ± 4	31 ± 5	<0.001
Waist circumference (cm)	94 ± 14	107 ± 13	<0.001
Ejection fraction (%)	63 (58–68)	64 (59–68)	0.17
Insulin (pg/mL)	5.4 ± 0.7	5.9 ± 0.6	<0.001
Hemoglobin A1c (%)	5.8 ± 1.1	6.1 ± 1.3	<0.001
Fasting glucose (mg/dL)	115 ± 41	125 ± 44	<0.001
LDL cholesterol (mg/dL)	103 ± 33	106 ± 34	0.25
HDL cholesterol (mg/dL)	48 ± 15	43 ± 12	<0.001
Triglycerides (mg/dL)	95 (67–147)	122 (82–175)	<0.001
C-reactive protein (mg/L)	1.8 (0.6–4.3)	2.6 (1.2–5.4)	<0.001
Creatinine (mg/dL)	1.0 (0.9–1.2)	1.1 (0.9–1.2)	0.002
Adiponectin (μg/mL)	25.9 (14.8–41.9)	18.0 (10.9–30.0)	<0.001

Values are expressed as number (% of category), median (IQR), or mean ± SD.

[*] p value by χ^2, Mann–Whitney or *t*-test.

[a] ARB, angiotensin receptor blocker.

subjects. Men had a lower median leptin level than women (6.8 versus 18.1 ng/mL; $p < 0.001$). Compared to participants with leptin levels above the sex-specific median, participants with lower leptin levels were more likely to smoke and to be physically active (Table 1). They were also less likely to have a history of hypertension, congestive heart failure, and diabetes. They were less likely to be on aspirin, ACE inhibitors or angiotensin receptor blockers, statins and diuretics. Subjects with low leptin levels had better metabolic profiles (lower body mass index, smaller waist circumference, lower insulin levels, lower hemoglobin A1c, lower fasting glucose, lower triglycerides, lower CRP, lower serum creatinine, higher HDL cholesterol, and higher adiponectin). There were no statistically significant differences between low and high leptin groups in terms of age, race, history of MI, history of stroke, alcohol use, beta-blocker use, blood pressure, ejection fraction, or LDL cholesterol.

3.1. Combined events

During 6105 person-years with a mean (SD) of 6.2 (2.1) years follow-up, a total of 304 deaths, 112 myocardial infarctions, 52 strokes/TIAs, and 370 combined events (MI, stroke/TIA or death) occurred. Fig. 1 shows distinct Kaplan–Meier event-free survival curves for the low and high leptin groups ($p = 0.01$ by log–rank
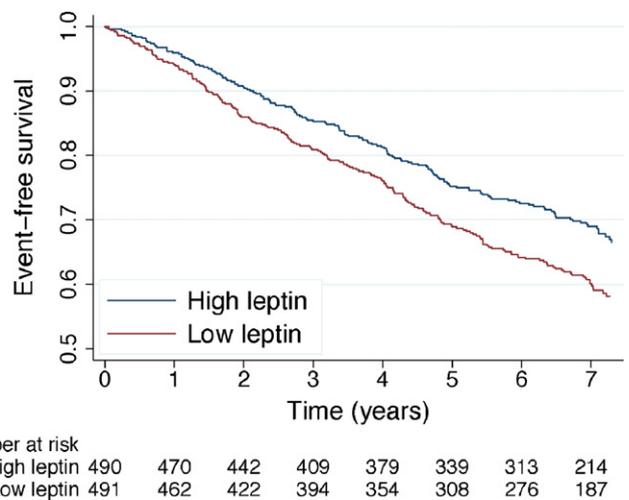

Number at risk								
High leptin	490	470	442	409	379	339	313	214
Low leptin	491	462	422	394	354	308	276	187

Fig. 1. Kaplan–Meier event-free survival curve, by high versus low leptin.

test). Among patients in the low leptin group, 42% (204/491) had an event (MI, stroke/TIA or death) compared with 34% (166/490) in the high leptin group (age- sex- and race-adjusted HR 1.3, CI 1.05–1.59, $p = 0.01$). This association persisted after adjustment for BMI and

Table 2
Association between leptin and cardiovascular events and mortality by Cox models.

| | Leptin low versus high | | | | | |
| | Combined events (MI, stroke/TIA, death) | | Nonfatal CV event | | All-cause mortality | |
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Model 1	1.30 (1.05–1.59)	0.01	1.26 (0.91–1.73)	0.16	1.26 (1.00–1.58)	0.05
Model 2	1.26 (0.99–1.60)	0.06	1.32 (0.90–1.91)	0.15	1.16 (0.89–1.50)	0.27
Model 3	1.29 (1.01–1.65)	0.04	1.37 (0.94–2.01)	0.10	1.14 (0.87–1.50)	0.34
Model 4	1.30 (1.01–1.67)	0.04	1.37 (0.93–2.02)	0.12	1.14 (0.86–1.50)	0.36
Model 5	1.37 (1.06–1.76)	0.02	1.51 (1.02–2.24)	0.04	1.17 (0.88–1.55)	0.29

Model 1: adjusted for age, sex, and white race.
Model 2: above plus BMI, waist circumference.
Model 3: above plus history of hypertension, congestive heart failure, diabetes, aspirin use, statin use, ACE inhibitor/ARB use, diuretic use, smoker, and physical activity.
Model 4: above plus diabetes, glucose, insulin, and hemoglobin A1c.
Model 5: above plus, creatinine, HDL, triglycerides, log–CRP, and adiponectin.

waist circumference (Table 2). In the fully adjusted model including demographic variables, clinical characteristics and biomarkers, low leptin was associated with a 37% increased risk of the combined outcome (HR 1.37, CI 1.06–1.76, $p = 0.02$). When leptin was analyzed as a continuous variable in the fully adjusted model, there was a 14% increase in risk of combined outcome for every standard deviation decrease in log–leptin, but this finding was not statistically significant (HR 1.14, CI 0.98–1.32, $p = 0.10$). The association between leptin and combined events was similar by sex, BMI, waist circumference, diabetes status, and adiponectin levels (all p values for interaction > 0.05).

3.2. Nonfatal CV events

In the low leptin group, 17% (84/491) had a nonfatal CV event (MI, stroke/TIA) compared with 14% (69/490) in the high leptin group (age- sex- and race-adjusted HR 1.26, CI 0.91–1.73, $p = 0.16$). In the fully adjusted model, low leptin was associated with a 51% increased risk of nonfatal CV event (HR 1.51, CI 1.02–2.24, $p = 0.04$). The association between leptin and nonfatal CV events was similar by sex, BMI, waist circumference, diabetes status, and adiponectin levels (all p values for interaction > 0.05).

3.3. All-cause mortality

Among patients in the low leptin group, 34% (166/491) died compared with 28% (138/490) in the high leptin group (age- sex- and race-adjusted HR 1.26, CI 1.00–1.58, $p = 0.05$). In the fully adjusted model, the association between low leptin and mortality was attenuated (HR 1.17, CI 0.88–1.55, $p = 0.29$). The association between leptin and mortality did not differ by waist circumference, sex, diabetes status, or adiponectin levels (p values for interaction > 0.05). However there was a statistically significant interaction between leptin and BMI when analyzed as continuous variables (p value for interaction = 0.009): when stratified by standard BMI categories, the association between leptin and mortality was strongest in the normal BMI range. In the normal BMI sub-

group, for every standard deviation decrease in log–leptin, there was a 63% increased risk of death (adjusted HR 1.63, CI 1.12–2.37, $p = 0.01$). To ensure this finding was not due to residual confounding, we compared the strength of association between BMI and leptin across the BMI strata (Table 4). In the normal and overweight BMI strata, there was no difference in the association between BMI and leptin (23% versus 22% increase in leptin per one unit increase in BMI, $p = 0.86$ for heterogeneity). In the obese BMI stratum, there was a 9% increase in leptin per one unit increase in BMI (CI 7–11%, $p < 0.001$), which was lower than the other BMI strata ($p < 0.001$ for heterogeneity). Even after adjusting for exact BMI within each BMI stratum, every standard deviation decrease in log–leptin was still associated with a 58% increased risk of death in the normal BMI subgroup (HR 1.58, CI 1.08–2.28, $p = 0.02$). In contrast, in the overweight and obese BMI subgroups, there was no statistically significant association between leptin and mortality (Table 3). The underweight subgroup (BMI < 18.5 kg/m^2) was excluded from these stratified analyses because there were only eight subjects in that category.

4. Discussion

In this prospective study of patients with stable CAD, we found that low baseline leptin levels predicted subsequent CV events and death. Although subjects with low leptin had fewer co-morbidities and more favorable metabolic and inflammatory profiles, they had a worse prognosis than subjects with high leptin. We also found that BMI modified the effect of leptin on mortality; lower leptin predicted mortality in patients with normal BMI but not in patients with high BMI. These findings provide insight into the potential role of leptin in cardiovascular disease.

Most prior studies on leptin and CAD have compared leptin levels in patients with and without CAD. A recent meta-analysis of these studies concluded that there is a modest association of high leptin with risk of incident CAD [7]. In contrast, we found an inverse association between leptin and CV events in patients with chronic CAD. One possible explanation for these findings is the

Table 3
Association of leptin with mortality, stratified by BMI.[a]

| | Per SD decrease in log–leptin[#] | | | |
| | Full model excluding BMI | | BMI-adjusted full model | |
	HR (95% CI)	p value	HR (95% CI)	p value
Normal weight (BMI 18.5–24.9 kg/m^2)	1.63 (1.12–2.37)	0.01	1.58 (1.08–2.28)	0.02
Overweight (BMI 25–30 kg/m^2)	0.86 (0.61–1.20)	0.36	0.83 (0.59–1.16)	0.27
Obese (BMI > 30 kg/m^2)	1.11 (0.76–1.63)	0.58	1.07 (0.74–1.55)	0.73

[a] Underweight (BMI < 18.5) excluded from stratified analyses due to insufficient numbers ($n = 8$).
[#] $p = 0.009$ for leptin × BMI interaction in entire cohort.

Table 4
Association of BMI with leptin across BMI categories.

	Number of subjects	% Increase in leptin per 1 unit increase in BMI (95% CI)	p value
Underweight (BMI < 18.5 kg/m^2)	$n = 8$	11% (−109% to 131%)	0.83
Normal (BMI 18.5–24.9 kg/m^2)	$n = 251$	23% (13–33%)	<0.001
Overweight (BMI 25–30 kg/m^2)	$n = 407$	22% (14–29%)	<0.001
Obese (BMI > 30 kg/m^2)	$n = 315$	9% (7–11%)[*]	<0.001

[*] $p < 0.001$ for heterogeneity between obese and other BMI categories.

concept of "reverse epidemiology" [21], whereby the association between a predictor and incidence of disease in the general population is reversed in patients with established disease. For example, although obese individuals are at increased risk for developing CAD, obesity is paradoxically protective in subjects with established CAD [22]. Thus, in patients with CAD, obese individuals have a better prognosis than non-obese individuals. "Reverse epidemiology" has also been described in the relationship between adiponectin and CAD [21]. Consistent with this hypothesis, another study showed that low leptin levels are associated with increased cardiovascular death in patients with chronic kidney disease [16].

Our findings raise the possibility that leptin may have a role in the obesity paradox. Leptin may be chronically upregulated as a compensatory response to CAD, yet at the same time have protective effects on long-term outcomes through specific signaling pathways. Multiple reports have shown that leptin causes coronary vasodilation, activates endothelial progenitor cells, prevents lipid accumulation, and protects against ischemia-reperfusion injury [4,6,23–25]. Hence in chronic CAD, relative leptin deficiency may predict a poorer prognosis.

The lack of association between leptin and mortality in patients with higher BMI could be explained by leptin resistance [26]. Leptin resistance increases with obesity, resulting in high circulating leptin levels but decreased leptin signaling, much like insulin resistance in type II diabetes. In subjects with normal BMI, the linear relationship between decreasing leptin and worse prognosis may be a true reflection of decreased leptin signaling. However, in overweight and obese subjects, perhaps there is more selective leptin resistance, and higher levels may actually reflect decreased effective signaling. As a result, the relationship between leptin levels and prognosis is not observed in high BMI subjects. Another explanation for this finding could be the dose-dependent nature of leptin's actions. In vitro studies have shown that leptin's effects at low dose may be opposite to its effect at higher doses [23]. Since obese individuals tend to have higher leptin levels, they may activate leptin signaling pathways that are distinct from non-obese people. Leptin also has central and peripheral actions, with distinct patterns of central and peripheral resistance, which further complicate the relationship between leptin and CAD [2].

There is one other prospective cohort study of leptin and prognosis in patients with existing CAD that followed 361 subjects with >10% stenosis on coronary angiography for 4 years [17]. However, this study reported opposite findings from our study: higher leptin predicted adverse outcomes (cardiac death, MI, stroke, or revascularization). One reason for the different findings may be the heterogeneity of their patient population, including both inpatients and outpatients. Their subjects ranged from minimal angiographic CAD (>10% stenosis) to acute coronary syndrome at enrollment, and it is possible that the effects of leptin in this higher acuity population are entirely different from our population of chronic stable CAD. Leptin is also an acute phase reactant and blood levels may rise in response to acute illness, which may not reflect the steady state [27]. They also excluded subjects with diabetes, prior coronary revascularization, or a smoking history >50 pack-years.

Among the strengths of our study is the prospective cohort design, with detailed characterization of demographic, clinical, and biochemical variables. However, several limitations should be considered. First, most subjects were older men and all were outpatients with stable CAD, so the findings may not generalize to women or other populations. In particular, leptin effects may be completely different in healthy subjects or those with acute coronary syndromes. Furthermore, leptin could be merely a marker of adiposity, and the BMI- and waist circumference-independent effects we found could be a result of residual confounding due to unmeasured confounders or because BMI and waist circumference are inadequate measures of adiposity. However, we did include two measures of obesity in hopes of more adequately capturing adiposity. Finally, this observational study cannot determine whether leptin plays an active role or is merely a passive bystander in CAD.

In summary, we found that low leptin levels predict subsequent adverse events independent of obesity and traditional cardiac risk factors in patients with stable CAD. We also found that the relationship between leptin and mortality is modified by BMI, which may be explained by increased leptin resistance in obesity. Whether leptin has direct protective effects in chronic CAD, or is a marker of other protective mechanisms, warrants further study. Understanding the effects of leptin in the CV system may provide insight into the relationship between obesity and heart disease.

Acknowledgements

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