

DIETARY SODIUM RESTRICTION ALTERS POSTPRANDIAL GHRELIN: IMPLICATIONS FOR RACE DIFFERENCES IN OBESITY

Objectives: To examine the effect of sodium restriction on the appetite-stimulating hormone, ghrelin, as a function of race, salt sensitivity, and obesity.

Design: Participants completed two 4-day outpatient dietary interventions (moderate vs low sodium), and blood samples were drawn two hours after a controlled test meal under both conditions.

Setting: A university research laboratory and affiliated General Clinical Research Center. Participants: 37 women (18 Black, 19 White) and 18 men (9 Black, 9 White), aged 36–63 years.

Measures: Cardiovascular function (blood pressure, heart rate, impedance-derived indices of cardiac output and peripheral resistance) was measured after a 20-minute rest before each test meal. Blood was drawn by intravenous forearm catheter two hours after each test meal and later assayed for ghrelin, leptin, and norepinephrine.

Results: After four days of sodium restriction, postprandial ghrelin increased in White men and women and Black men but decreased in Black women. Salt sensitivity, but not obesity, was also related to ghrelin response during sodium restriction; postprandial ghrelin tended to increase among salt-sensitive subjects during salt restriction but decrease among salt-resistant subjects during salt restriction.

Conclusions: Satiety hormone dysregulation may play a role in: 1) the heightened obesity-related morbidity among Black women, in particular; 2) adherence to sodium-restricted diets; and 3) race differences in behavioral weight-loss interventions that include sodium restriction. (*Ethn Dis.* 2006;16:844–851)

Key Words: Appetite, Gender, Ghrelin, Obesity, Race, Salt

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INTRODUCTION

In the previous decade, obesity increased 61% among US adults,¹ and non-Hispanic Blacks bore the largest burden of that increase. In the United States, Blacks are nearly two times more likely to be obese than Whites, and Black women experience the highest rates of obesity (49%) overall. Compared to their White counterparts, Black women are also especially vulnerable to obesity-related cardiovascular and metabolic complications such as hypertension and diabetes.² Reasons for these ethnic disparities in obesity and its comorbid conditions are not fully understood; however, recent work suggests differences in short-term appetite regulation may play a role.

Ghrelin is a peptide hormone with appetite-stimulating and adipogenic properties.^{3,4} In contrast to leptin, which modulates energy intake on a longer-term basis by responding to fluctuations in adipose stores, ghrelin provides a short-term “need to eat” signal and has been referred to as the “hunger hormone.”^{5,6} Ghrelin appears to be involved in meal initiation, as plasma ghrelin levels increase shortly before and decrease precipitously after food intake.^{7–9} The plasma ghrelin level typically remains suppressed for several hours during the postprandial period of

satiation. Failure to maintain postprandial ghrelin suppression after meal intake may render an individual more susceptible to eating again soon.¹⁰ Previously, we observed higher postprandial ghrelin in Black compared to White women, and obese Black women had the highest postprandial ghrelin levels overall.¹¹

In addition to its role in appetite regulation, ghrelin has direct vasodilatory properties and modulates cardiovascular functioning.^{12–16} Thus, interest is growing in articulating ghrelin’s role in the cardiovascular complications of obesity-related diseases. In our previous report, higher postprandial ghrelin in Black women was associated with higher 24-hour cortisol, which is a common finding in obesity.^{17,18}

Obesity often co-occurs with hypertension, and both are hallmarks of the constellation of overlapping disorders known as the metabolic syndrome. Obesity hypertension is linked to various metabolic and endocrine abnormalities, including sodium sensitivity.^{19,20} Thus, weight reduction and salt restriction are the first two treatment options considered by many practi-

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tioners for individuals who are overweight and/or have borderline-to-mild hypertension. Salt sensitivity frequently co-exists with disturbances in insulin and leptin regulation,^{21–25} and salt sensitivity is more common in Blacks. To date, no studies have examined whether salt intake and/or salt sensitivity affect ghrelin and whether the relationship between salt sensitivity and ghrelin differs among ethnic groups. Therefore, the purpose of our study was to examine the effects of sodium restriction on ghrelin and on related markers of cardiovascular and metabolic function in a biracial sample of men and women.

METHODS

Subjects

This study is based on 37 women (22 postmenopausal, 11 using hormone therapy) and 18 men, aged 36–63 years, who completed a study of dietary sodium and blood pressure (BP), which was approved by the local biomedical ethics committee. The 37 women are a subset of those examined in our previous publication on postprandial ghrelin.¹¹ No subject was using antihypertensive medication, and all were otherwise healthy.

Procedures

Details of the procedures are available elsewhere¹¹ and specifics for this study are described below.

Dietary Intervention

Each participant completed two counterbalanced four-day controlled dietary interventions that differed in sodium content (moderate=220 mEq/day vs low=50 mEq/day) but were matched for potassium (40 mEq/day) and macronutrient content (\approx 60% carbohydrate, 28% fat, 12% protein). General Clinical Research Center staff planned and prepared all meals, which were adjusted for body size.

Standardized Testing Protocol

On day 4 of each diet, participants completed a 4.5-hour laboratory session that began between 4:30 and 6:30 p.m., during which they consumed a standardized dinner, underwent a two-hour period of controlled water drinking and urine collection to promote a steady state of hydration and sodium excretion, and were evaluated for resting cardiovascular and neuroendocrine activity.

Cardiovascular and Hormone Measures

During a 20-minute rest period at the end of the two-hour hydration stabilization period, BP was measured by using an automated device, and cardiac performance was measured by using impedance cardiography, which allowed us to estimate cardiac output (CO) and total peripheral resistance (TPR). Cardiac output (CO), TPR, and stroke volume measures were adjusted for differences in body size²⁶ to yield measures of cardiac index (CI), vascular resistance index (VRI), and stroke volume (SVI) index. At the conclusion of the two-hour stabilization period, blood samples were drawn to assess postprandial levels of ghrelin, leptin, and norepinephrine.

Bioassays

Blood samples were drawn into pre-chilled, EDTA-containing tubes, centrifuged, and stored at -80°C . Plasma levels of active acylated ghrelin were measured by a competitive enzyme immunoassay (EIA; Peninsula Labs, Belmont, Calif), with a sensitivity of .08 ng/mL (standard range of 0–25 ng/mL) and intra- and inter-assay variations of 5% and 14%, respectively. Total (bound and free) leptin was measured in unextracted plasma by competitive EIA (Peninsula Labs), with a sensitivity of .4 ng/mL (standard range of 0–500 ng/mL) and intra- and inter-assay variations of 7% and 10.2%, respectively. Plasma norepinephrine was determined using high performance liquid chromatography with electrochemical detection.

Statistical Analysis

Average values for cardiovascular variables were calculated as the mean of minutes 15, 17, and 19 of the rest period. Ghrelin, leptin, and norepinephrine data were log-transformed before analysis. Salt sensitivity was determined based on BP change during the low-sodium diet (≥ 5 mm Hg reduction in mean arterial pressure [MAP]=“salt sensitive” [SS]; all others=“salt resistant” [SR]). Obesity was defined as a body mass index (BMI) ≥ 30 kg/m².

In preliminary analyses, diet-related (moderate minus low salt) changes in plasma volume correlated with changes in leptin ($r=.41$, $P<.002$) and changes in norepinephrine ($r=.36$, $P<.008$), but not with changes in ghrelin ($r=.13$, $P>.34$). In addition, independent of the effects of plasma volume, changes in norepinephrine, leptin, and ghrelin, were each correlated with their initial (ie, moderate-salt diet) levels ($r=.28$ to $.63$, $P<.05$). Therefore, all primary analyses involving norepinephrine, leptin, and ghrelin were adjusted for initial hormone levels, and those involving norepinephrine and leptin were also adjusted for changes in plasma volume.

The effect of sodium restriction on postprandial hormone levels was evaluated separately by sex with repeated measures analysis of covariance; diet was the repeated factor, and race (Black, White), salt sensitivity (sensitive, resistant), or obesity (obese, non-obese) were between-subjects factors. All analyses were carried out by using SAS v.8.0 software (SAS, Cary, NC). Results were expressed as the mean plus or minus standard deviation [SD] unless otherwise stated. $P<.05$ was considered statistically significant.

RESULTS

Sodium Restriction Effects on Resting Sympathetic Function

As seen in the Table, sodium restriction reduced MAP in women

Mean (SD) age, BMI, and resting sympathetic function by sex, race, and diet

	Women		Men	
	Black	White	Black	White
<i>n</i>	18	18	9	9
Age (years)	46.0 (7.6)	48.6 (7.1)	43.0 (5.1)	43.4 (5.3)
BMI (kg/m ²)	32.4 (5.1)	28.0 (5.7)	29.4 (4.8)	26.5 (4.8)
MAP (mm Hg)				
Moderate salt	99.8 (12.3)	88.6 (8.6)	100.5 (10.9)	98.5 (9.1)
Low salt	93.8 (12.5)	82.5 (7.9)	87.2 (7.2)	91.3 (9.1)
VRI (dyne-sec × cm ⁻⁵ × m ²)				
Moderate salt	2820.1 (1094.1)	2333.7 (606.2)	3339.0 (1462.0)	2484.8 (666.6)
Low salt	2734.0 (935.5)	2017.0 (519.9)	2669.8 (1409.8)	2414.1 (913.2)
Cardiac index (L/min/m ²)				
Moderate salt	3.3 (1.4)	3.2 (.8)	2.9 (1.4)	3.4 (1.0)
Low salt	3.1 (1.1)	3.5 (.8)	3.4 (1.7)	3.3 (1.0)
Stroke volume index (mL/m ²)				
Moderate salt	41.8 (16.8)	44.2 (11.6)	40.5 (20.8)	45.6 (14.2)
Low salt	38.3 (12.6)	47.1 (13.2)	43.6 (22.8)	43.3 (10.3)
Heart rate (bpm)				
Moderate salt	78.2 (9.8)	79.7 (7.5)	72.9 (6.9)	75.1 (8.0)
Low salt	72.8 (11.4)	74.3 (11.8)	77.6 (5.8)	75.9 (9.9)
Norepinephrine (pg/mL)				
Moderate salt	259.4 (137.6)	308.7 (189.3)	296.0 (127.4)	257.2 (118.7)
Low salt	214.5 (100.6)	227.6 (108.5)	331.2 (52.2)	264.9 (113.0)

SD= standard deviation; BMI= body mass index; MAP= mean arterial pressure; VRI= vascular resistance index; bpm= beats per minute.

[F(1,35)=34.05] and in men [F(1,16)=37.78], $P<.0001$, because of underlying reductions in VRI [women, F(1,34)=4.80, $P<.04$; men, F(1,16)=5.56, $P<.04$]. Plasma norepinephrine increased in men [F(1,13)=13.31, $P<.003$], primarily because of Black men [diet × race effect, $P<.04$]. Women showed a nonsignificant trend toward increased norepinephrine after sodium restriction ($P>.11$).

Effects of Sodium Restriction on Postprandial Satiety Hormone Levels

Women

As in the larger sample of 43 women,¹¹ postprandial ghrelin and leptin were higher among Black than among White women under the moderate sodium condition (ghrelin: Black=.33 ± .16, White=.26 ± .13; leptin: Black=55.7 ± 35.1, White=25.8 ± 25.7). As seen in Figure 1, sodium restriction affected postprandial

ghrelin differently in Black and White women [diet × race effect, F(1,39)=10.72, $P<.003$], and this effect remained after adjusting for initial ghrelin level ($P<.04$). Postprandial ghrelin increased in White women ($P<.02$) and decreased in Black women ($P<.05$) after sodium restriction (Fig 1A). Leptin increased after sodium restriction [diet effect, F(1,40)=11.08, $P<.002$], and this effect was strengthened after adjusting for plasma volume changes and initial differences in leptin level ($P<.0001$). Leptin changes after sodium restriction did not differ as a function of race ($P>.48$; Fig 1B).

Men

As seen in Figure 1C and 1D, ghrelin and leptin levels, which were initially similar in Black and White men ($P>.89$), increased in both groups after sodium restriction [ghrelin, F(1,17)=4.96, $P<.04$; leptin, $P<.07$].

In summary, after a four-day low-sodium diet, resting MAP and periph-

eral vascular resistance were reduced, whereas resting norepinephrine and postprandial leptin were increased among all four subgroups. Postprandial ghrelin increased among men and White women but decreased among Black women.

Effect of Salt Sensitivity on Hemodynamic and Hormonal Responses to Salt Restriction

By definition, compared to SR subjects ($n=18$), SS subjects ($n=37$) showed greater reductions in MAP (.2 ± 1.0 vs -11.1 ± .7 mm Hg, $P<.0001$); VRI was also reduced to a greater extent in SS (-197.98 ± 47.32) vs SR (18.69 ± 66.93) subjects ($P<.02$) after sodium restriction. Salt sensitive (SS) individuals were equally represented by race [$\chi^2=.2$, $P>.63$] and by sex; however, we found disproportionately fewer SR men than women ($\chi^2=5.7$, $P<.02$). Ten of 18 Black women, 11 of 19 White women, 9 of 9 Black men, and 7 of 9 White men were SS.

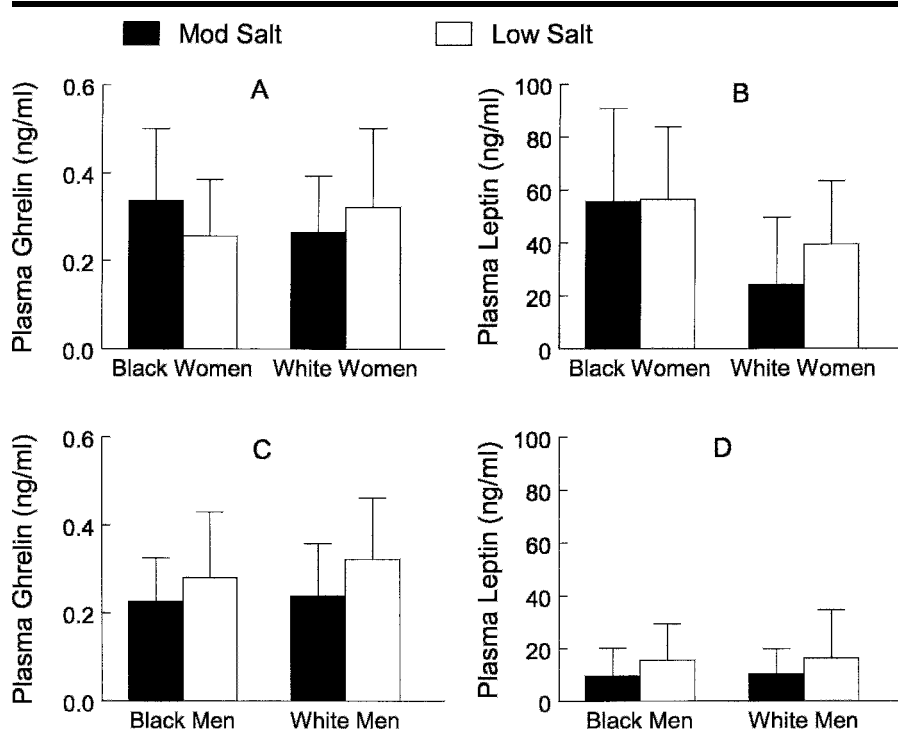


Fig 1. Two-hour postprandial mean (standard deviation [SD]) plasma ghrelin (left panels) in Black and White women (1A) and men (1C) and two-hour postprandial mean (SD) plasma leptin (right panels) in Black and White women (1B) and men (1D) after four days on a moderate-salt (solid bar) vs low-salt (open bar) diet

The change in ghrelin following sodium restriction differed according to salt sensitivity [diet \times salt sensitivity, $F(1,53)=5.58$, $P<.03$]. On average, postprandial ghrelin tended to decrease after sodium restriction among those who were SR and to increase among those who were SS (Figure 2). This effect remained intact after adjusting for initial ghrelin level ($P<.05$) and was strengthened by adjusting for race ($P<.03$), which suggests independence between the effect of race and the effect of salt sensitivity on changes in ghrelin after sodium restriction. Equal numbers of Black women were SS and SR. Given the small number of SR men, sex differences in this effect were not tested. However, it was significant within the subgroup of women only [diet \times salt sensitivity, $F(1,33)=4.74$, $P<.04$], and both men and women who were SS tended toward increased ghrelin after sodium restriction [men: $.22 \pm .10$ ng/

mL (moderate salt) vs $.30 \pm .15$ ng/mL (low salt); women: $.29 \pm .12$ ng/mL (moderate salt) vs $.34 \pm .17$ ng/mL (low salt)].

In contrast, salt sensitivity was not a significant factor underlying the increases in leptin and norepinephrine that followed sodium restriction, either in the overall sample ($P>.30$) or in women only ($P>.13$) (data not shown).

Effect of BMI on Ghrelin Responses to Sodium Restriction

Twenty-one subjects (17 female) were obese. Analyses of the impact of obesity on hormonal changes after sodium restriction were limited to the sample of women. Body mass index (BMI) was higher in Black (33.1 ± 5.8 kg/m²) compared to White (28.4 ± 5.8 kg/m²) women [$F(1,36)=6.04$, $P<.02$], but BMI was not correlated with the change in ghrelin after sodium restriction in either group ($P>.67$). As

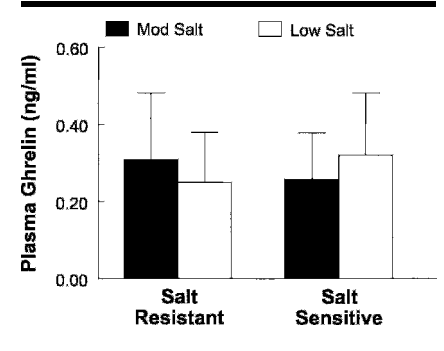


Fig 2. Two-hour postprandial mean (standard deviation) plasma ghrelin levels in salt-resistant and salt-sensitive subjects after four days on a moderate-salt (solid bar) vs low-salt (open bar) diet

noted, after sodium restriction, Black women tended to exhibit a decrease in ghrelin and White women tended to show an increase in ghrelin, resulting in a significant race \times diet interaction. This interaction effect remained intact after adjusting for BMI [$F(1,34)=4.11$, $P<.05$] and as shown in Figure 3, these effects were consistent across BMI groups in both Black and White women.

DISCUSSION

Age, sex, BMI, sleep, and macronutrient content influence plasma ghrelin concentration.²⁷⁻³¹ To our knowledge, the current study is the first to show that ghrelin is sensitive to dietary sodium intake.

Previously, we reported that Black women (particularly obese Black women) exhibited elevated postprandial ghrelin and leptin, BP, and vascular

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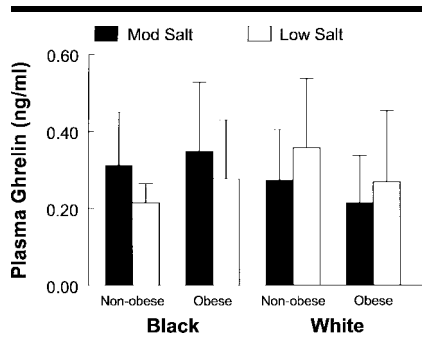


Fig 3. Two-hour postprandial mean (standard deviation) plasma ghrelin levels in Black and White non-obese and obese women after four days on a moderate-salt (solid bar) vs low-salt (open bar) diet

resistance compared to White women.¹¹ Moreover, postprandial ghrelin level correlated highly with 24-hour urinary cortisol only in Black women, suggesting perhaps that alterations in the control of ghrelin secretion may be a sign of a more generalized hypothalamic dysregulation in this group. A highly representative subset of these same women, along with a sample of Black and White men, underwent hormonal and cardiovascular assessments after four days of sodium restriction, the results of which are the focus of this current report. After sodium restriction, White women and men and Black men exhibited increases in postprandial ghrelin. In contrast, Black women exhibited a decrease in postprandial ghrelin after sodium restriction. This newest observation provides a second indication from our controlled dietary studies of a ghrelin response to dietary manipulation that appears to differentiate Black women from other race/sex subgroups. The extent to which this difference contributes to differences in appetite and energy intake and to the increased risk of obesity among Black women is not yet clear.

Leptin significantly increased after sodium restriction in the overall sample. Ghrelin and leptin are intrinsically

balanced and their signals centrally integrated²⁹; however, the precise relationship between ghrelin and leptin remains the subject of considerable debate.³² Both are reciprocally regulated by perturbations in energy balance, but in response to such perturbations they exert opposite central effects.³³ The increase in leptin observed in most subjects may represent a compensatory response designed to inhibit the pro-feeding effects of elevated postprandial ghrelin. If confirmed, the tendency toward elevated leptin in the face of decreased postprandial ghrelin after sodium restriction may suggest some disruption in the interplay between these two highly responsive systems in Black women. Such a breakdown in communication may constitute a part of the machinery underlying leptin overproduction and the eventual development of leptin resistance that is common in obesity and implicated in its sympathetically mediated cardiovascular complications.^{34,35}

Salt restriction is a mainstay of dietary recommendations for controlling hypertension.³⁶⁻³⁸ However, chronic and extreme salt restriction may actually increase cardiovascular morbidity and mortality.³⁹ Reasons for these adverse effects are not entirely clear but may reflect a constellation of factors, including decreased glucose uptake, insulin sensitivity, and adipose tissue fatty acid synthesis,^{24,40} as well as increased plasma renin activity and insulin and norepinephrine levels.⁴¹⁻⁴³ The current study adds to this list by demonstrating post-sodium restriction alterations in satiety and energy-regulating hormones that may contribute directly to weight dysregulation and secondarily to increased cardiovascular risk. The extent to which these effects account for ethnic differences in sodium-related hypertension and obesity is unclear.

When dietary sodium intake is low, Blacks and Whites tend to show similar degrees of sodium retention.^{44,45} None-

theless, low-sodium dietary interventions tend to elicit greater BP reductions in Blacks than in Whites.^{46,47} In contrast, behavioral weight-loss programs may be more effective in Whites than in Blacks,⁴⁸⁻⁵⁰ and Black women experience the smallest net weight loss overall.⁴⁸ A recent study in elderly subjects⁵¹ suggests that the addition of a sodium-reduction component to a behavioral weight-loss regimen negates this advantage in Whites, largely because Whites lose less weight under combined calorie and sodium restriction than under calorie restriction alone. The present findings are consistent with the notion that Whites may lose less weight when trying to restrict sodium because of increases in ghrelin that generate an earlier postprandial hunger signal leading to increased food intake.

Sodium deficiency can trigger an increase in salt appetite.⁵² Salt appetite is a highly adaptive homeostatic response designed to restore and maintain sodium and fluid balance, which is essential for optimal functioning of an array of physiologic processes. Depletion of extracellular fluid, in particular, mobilizes salt appetite, and in rats, resolving a deficit in extracellular fluid requires both drinking water and consuming salt. In part, decrements in arterial BP, which generate a reflex release of vasopressin and increased sympathetic nervous system activity, also stimulate increased salt intake. While less studied in humans, this finding suggests an increase in salty food intake that may, for some individuals, equate with an increase in calories. Studies that elucidate ethnic and sex differences in food-intake patterns during sodium restriction are needed to address this question. The observed ghrelin and leptin responses to salt-restricted meals may be factors in the familiar phenomenon of "salt craving" and may also help explain why many individuals fail to stay on low-salt diets.^{53,54}

In the present study, the ghrelin response to moderate- vs low-salt meals

was similar in obese and non-obese individuals but tended to differ between SS and SR subjects; SS individuals tended to show elevations in ghrelin after salt restriction. Salt sensitivity has been linked to insulin sensitivity and to leptin resistance. Compared to those who are SR, SS individuals tend to be hyperinsulinemic or more insulin resistant.^{25,55,56} In addition, leptin-resistant, obese, spontaneously hypertensive rats show pronounced salt sensitivity.^{22,23,57} The present findings suggest that salt sensitivity (independent of ethnicity and body mass) may uniquely predispose an individual toward satiety hormone disturbances that ultimately may promote hyperphagia and weight gain. In this regard, ghrelin dysregulation may be a novel link between salt sensitivity, leptin and insulin resistance, hypertension, and obesity and a co-conspirator in the metabolic syndrome.

The strengths of this study include the novel examination of dietary sodium as a potential modifier of ghrelin under "naturalistic" conditions (ie, after a four-day controlled diet representative of local and regional dietary intake)⁵⁸ and the carefully regulated timing of the postprandial metabolic and cardiovascular measurements. A major limitation of this study is the absence of pre-meal and more frequent post-meal ghrelin assessments. As such, we cannot say whether sodium affects basal ghrelin levels, immediate pre-meal levels, postprandial suppression or rebound, or some combination thereof. Other limitations include the absence of 1) insulin and insulin resistance measures to help characterize participants' metabolic status and 2) assessments of psychological, social, or environmental factors known to influence appetite and dietary compliance that may have accounted for some variability in our outcome measures. Such data will likely be important to understanding ethnic and sex differences in ghrelin responses to dietary manipulation and whether such differences ultimately play a role in the

preponderance of obesity and obesity-related cardiovascular morbidity among African American women, in particular.

In summary, after four days of sodium restriction, postprandial ghrelin increased in White men and women and in Black men but decreased in Black women. Salt sensitivity, but not obesity, was related to ghrelin response during sodium restriction; postprandial ghrelin tended to increase among SS subjects but decrease among SR subjects during salt restriction. These effects did not appear to merely reflect alterations in hormone plasma concentrations. These findings extend our previous observations that Blacks exhibit a pattern of physiologic responses that may contribute to increased cardiovascular disease risk, including increased vascular resistance and slowed sodium excretion during stress.⁵⁹⁻⁶¹ The current findings are consistent with the notion that satiety hormone dysregulation may play a role in: 1) the heightened obesity-related morbidity among Black women, in particular; 2) adherence to sodium-restricted diets; and 3) reduced weight loss in White adults in behavioral weight-loss interventions that include sodium restriction. Further investigation of ethnic and sex differences in ghrelin response to sodium (and other electrolyte) manipulation, and of the impact of such differences on obesity and cardiovascular morbidity, is warranted.

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