

Does sympathoadrenal activity predict changes in body fat? An 18-y follow-up study^{1–3}

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ABSTRACT

Background: Whether alterations in the sympathoadrenal system contribute to obesity or, rather, are consequences of it, is an unresolved issue.

Objective: We hypothesized that the sympathoadrenal system plays a predictive role in the development of body fat.

Design: At entry, arterial plasma epinephrine and norepinephrine concentrations were measured in 99 healthy men ($\bar{x} \pm$ SD age: 19.3 \pm 0.4 y) at rest and during a mental stress test and a cold pressor test. Body mass index (BMI; in kg/m²), waist circumference, and triceps skinfold thickness were measured at entry and after 18 y of follow-up.

Results: Eighty subjects (81%) were available for follow-up analyses after a mean (\pm SD) of 18.0 \pm 0.9 y. The epinephrine responses to the mental stress test (E_{MST}) showed a negative relation to changes in BMI ($P = 0.01$) and waist circumference ($P = 0.007$). The mean increase in BMI was 6.3 among subjects in the lowest E_{MST} quartile and 3.7 in the remaining subjects. In multiple regression analyses corrected for level of exercise, BMI, waist circumference, and triceps skinfold thickness at entry, E_{MST} was found to be a consistent negative predictor of future BMI ($P = 0.005$), waist circumference ($P = 0.001$), and triceps skinfold thickness ($P = 0.05$).

Conclusions: We present the first long-term follow-up study in whites showing that the epinephrine response to mental stress is a negative predictor of future BMI, waist circumference, and triceps skinfold thickness after 18 y of follow-up. These findings may provide further insights into the pathophysiology of obesity. *Am J Clin Nutr* 2008;87:1596–601.

INTRODUCTION

Obesity and overweight are of growing worldwide concern and reaching epidemic proportions (1). Obesity is a strong predictor of mortality (2), and it was recently shown that overweight is related to increased mortality (3). Animal and twin studies indicate that 25–40% of the variability in human body weight may be accounted for by genetic factors (4), and the sympathoadrenal system and β -adrenergic receptors are thought to play an important role (5–7). However, whether alterations in the sympathoadrenal system contribute to obesity or, rather, are consequences of it, is still an unresolved issue (8) because most of the data available are from cross-sectional studies. Only 2 longitudinal studies have been performed. Tataranni et al (9) studied 44 Pima Indians over a period of 3.3 y, assessing the predictive power of 24-h urinary catecholamine excretion rates. They found that baseline epinephrine excretion was negatively related to

changes in the waist-to-thigh circumference ratio, whereas norepinephrine excretion correlated negatively with body weight gain. Masuo et al (10), on the other hand, found resting plasma norepinephrine to be a positive predictor of changes in body mass index (BMI; in kg/m²) over a 5-y period in 433 Japanese subjects. Hence, the available data are contradictory, and the follow-up periods are short. Moreover, there are no longitudinal data on whites. The Pima Indian population has one of the highest prevalences of obesity in the world. They have lower muscle sympathetic nervous activity (11) and a lower chronotropic sensitivity to β -adrenergic stimulation than do whites (12). Thus, findings in studies on this population cannot be generalized to whites.

The present 18-y follow-up study investigated the predictive role of sympathoadrenal activity in the development of body fat in whites. We hypothesized that arterial plasma epinephrine and norepinephrine at rest and during laboratory stress were related to the increase in BMI, waist circumference, and triceps skinfold thickness. We also examined whether reactivity to 2 separate stress tests, a cold pressor test and a mental stress test, would differ in their predictive power. The 2 tests are supposed to represent different reactivity mechanisms, α - compared with β -adrenergic responses, respectively (13).

SUBJECTS AND METHODS

Participants

The local Ethics Committee approved the study, and the procedures followed were in accordance with institutional guidelines. Informed consent was obtained from each subject both at entry and at follow-up. All 19-y-old men in Norway are required to undergo a medical examination as part of the military draft procedure. The participants were seated for 5 min and then a

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trained physician measured blood pressure (BP) once with an automatic auscultatory device (Boso-digital II S; Bosh & Sohn GmbH, Jungingen, Germany) or a newly calibrated mercury sphygmomanometer. None of the subjects were informed about the results of the BP recordings at this stage, to avoid effects of hypertension labeling on responses to the stress tests (14, 15). Mean BP was thereafter calculated as diastolic BP + pulse pressure/3.

A total of 99 subjects were selected from the military draft screening: 30 were in the 1st percentile, 30 were in the 50th percentile, and 39 were in the 95th–99th percentile of the mean BP distribution. This selection procedure was followed to ensure a good representation of BP readings, because BP is related to sympathoadrenal activity (16). All subjects were white, except one who was half Asian and half white. The subjects were healthy and had no history of diabetes, renal disease, elevated BP, or other cardiovascular disease and had normal results from a physical examination, electrocardiogram, routine blood tests, and urinalysis. None of the subjects were receiving medical treatment or abused drugs or alcohol.

Examination at entry

The protocol at baseline is described in detail elsewhere (17) and was performed in 1986–1989. Resting heart rate and BP were recorded after the subjects had rested for 15 min in a sitting position; the same equipment used during the screening was used. Height, weight, and waist circumference were measured while the subjects were standing. BMI was calculated as weight (kg) divided by height² (m). Waist circumference was measured in 34 subjects at entry. Skinfold-thickness measurements were performed with a Harpenden skinfold caliper. A fold of skin, including subcutaneous tissue, was seized between thumb and forefinger, half-way down the triceps. The mean of 2 measurements was used. A short Teflon catheter (Venflon, 19G; Viggo AB, Hälisingborg, Sweden) was introduced under local anesthesia without epinephrine (Xylocain; AstraZeneca, Wilmington, DE) into the left brachial artery for blood sampling.

The cold pressor test lasted for 1 min. The right hand was completely immersed in ice water (0–2 °C). During the mental arithmetic test, the subjects were asked to subtract the number “13” repetitively starting from “1079” for 5 min, while a metronome made noise at a frequency of 2 Hz. They were informed about any miscalculation. After each test there was a 30-min recovery period. Arterial blood for catecholamine assay was collected after 30 min of supine rest, before and during the cold pressor test (after 0.5 and 1 min), and before and during the mental stress test (after 1, 3, and 5 min). Catecholamine responses to stress tests were calculated as the mean value during stress, subtracting the baseline value before the test. Blood was drawn into 2-mL glass tubes containing glutathione and EGTA, and plasma catecholamines were measured with a radioenzymatic technique according to Peuler and Johnsen (18) as previously reported (15, 19). All the blood samples were analyzed by the same technician.

Examination at follow-up

Follow-up examinations were conducted from 2005 to 2006. The mean (\pm SD) length of follow-up was 18.0 ± 0.9 y; 81 of the original 99 subjects (82%) were available for examination at follow up. A total of 18 subjects were not reexamined; 1 was

excluded because of probable intravenous drug addiction, 2 lived abroad and were not able to attend the examinations, 4 did not answer any letters or calls, and 11 did not want to participate. The subjects that were not available for follow-up did not differ from the reexamined subjects in resting BP, heart rate, BMI, waist circumference, or catecholamine stress responses at entry. One subject who was reexamined had ulcerative colitis and had to be excluded from further analyses because of a previous colectomy and an excessive intake of water and salt.

At follow-up, 21 subjects (25.9%) reported having one or more of the following diseases: hypertension ($n = 9$), hypercholesterolemia ($n = 12$), diabetes mellitus ($n = 3$), and myocardial infarction ($n = 1$). Eight of these subjects used one or more of the following medications regularly: angiotensin receptor blockers ($n = 3$), β -blockers ($n = 3$), angiotensin-converting enzyme inhibitor ($n = 1$), statins ($n = 2$), antidiabetics ($n = 3$), and acetylsalicylic acid ($n = 1$).

Each subject was studied in the same room at 0800 each day after fasting overnight. They abstained from any medication use or smoking for 8 h before and from alcohol for 24 h before the examination. BMI, waist circumference, and triceps skinfold thickness were measured and calculated in the same way as at entry.

Resting BP was measured 3 times on the left arm after the subjects had sat for ≥ 15 min, and was calculated as the mean of the last 2 measurements. Standardized questionnaires were used to collect information about concomitant diseases, medication, family history, education, occupation, and exercise. Baseline blood samples were drawn after a minimum of 30 min of supine rest.

Statistics

The data were analyzed by using the statistical package SPSS version 14.0 for WINDOWS (SPSS Inc, Chicago, IL). Paired-samples *t* tests were used to analyze possible changes in normally distributed continuous variables from entry to follow-up, and the Wilcoxon’s signed ranked test was applied when normality was not achieved by log-normal transformation. Categorical variables were analyzed by sign test. Associations between continuous variables were assessed by using Pearson’s correlations, whereas chi-square testing with linear-by-linear association was used for dichotomous variables.

To adjust for possible confounders, linear regression analysis was performed with BMI, waist circumference, and triceps skinfold thickness at follow-up as dependent variables and level of exercise at follow-up and selected variables measured at entry as independent variables. Exercise was graded in 3 levels: 1, <1 h of exercise per week; 2, >1 h of moderate exercise per week; and 3, >1 h of heavy exercise a week. The data are presented as means \pm SD unless otherwise indicated. Null hypotheses were rejected if the 2-tailed *P* value was <0.05 .

RESULTS

Descriptive characteristics

Characteristics of the participants at baseline and follow-up are presented in **Table 1**. They were 19.3 y of age (range: 18.2–20.8 y) on the first visit, and 37.3 y (range: 35.4–38.9 y) by the time of the reexamination. Systolic BP ($P = 0.003$) and diastolic



TABLE 1Descriptive characteristics at entry to the study and after 18 y of follow-up¹

Characteristic	No. of subjects	Entry		Follow-up	
Age (y)	80	19.3 ± 0.4 ²	37.3 ± 0.8 ³		
Systolic blood pressure (mm Hg)	76	126 ± 20	131 ± 16 ⁴		
Diastolic blood pressure (mm Hg)	76	70 ± 17	89 ± 10 ³		
Heart rate (beats/min)	75	66 ± 15	64 ± 12		
BMI (kg/m ²)	80	22.4 ± 3.0	26.7 ± 4.3 ³		
Waist circumference (cm)	34	83.0 ± 8.6	94.5 ± 11.1 ³		
Triceps skinfold thickness (mm)	70	10.0 ± 4.2	12.2 ± 6.1 ³		
Total serum cholesterol (mmol/L)	79	4.0 ± 0.7	4.9 ± 0.9 ³		
Serum HDL cholesterol (mmol/L)	78	1.1 ± 0.2	1.2 ± 0.3		
Serum triacylglycerols (mmol/L)	79	0.8 ± 0.4	1.3 ± 0.9 ³		
Plasma glucose (mmol/L)	69	4.2 ± 0.5	5.1 ± 0.8 ³		
Daily smokers [n (%)]	78	28 (36)	20 (26)		
Epinephrine during rest (pg/mL)	80	45.8 ± 31.4	—		
Epinephrine during MST (pg/mL)	67	116.1 ± 76.8	—		
Epinephrine during CPT (pg/mL)	74	78.5 ± 48.5	—		
Norepinephrine during rest (pg/mL)	80	118.5 ± 56.7	—		
Norepinephrine during MST (pg/mL)	68	193.9 ± 78.1	—		
Norepinephrine during CPT (pg/mL)	74	156.4 ± 75.3	—		

¹ Blood samples were collected after the subjects fasted overnight. Catecholamines represent arterial plasma concentrations. MST, mental stress test; CPT, cold pressor test. Paired-samples *t* tests were used for normally distributed variables, Wilcoxon's signed-rank test was used when normality was not achieved by log-normal transformation, and the proportions of smokers were compared by using a sign test.

² $\bar{x} \pm$ SD (all such values).

^{3,4} Significantly different from entry: ³ $P < 0.001$, ⁴ $P < 0.05$.

BP ($P < 0.001$) increased significantly, as did BMI, waist circumference, triceps skinfold thickness, serum cholesterol, serum triacylglycerol, and fasting plasma glucose (all $P < 0.001$).

Catecholamines and cardiovascular disease risk factors at entry

There were no significant relations between cardiovascular disease risk factors, the resting epinephrine concentration, or the epinephrine response to the mental stress test at entry (**Table 2**). The epinephrine response to the cold pressor test was positively related to resting diastolic BP ($r = 0.39$, $P = 0.001$). Smoking was positively related to resting norepinephrine ($P = 0.008$) and negatively related to the norepinephrine response to mental stress ($P = 0.004$). BMI, waist circumference, and triceps skinfold thickness at entry did not correlate with any of the catecholamine variables.

Prediction of 18-y changes in BMI, waist circumference, and triceps skinfold thickness

The absolute epinephrine response to mental stress at entry was negatively related to the changes in BMI ($r = -0.31$, $P = 0.01$), waist circumference ($r = -0.49$, $P = 0.007$), and triceps skinfold thickness ($r = -0.22$, $P = 0.10$) after 18 y. A threshold between the first and second stress response quartile is suggested in **Figure 1**. Whereas the mean BMIs at entry and follow-up were 22.1 and 28.4, respectively, in the first quartile, the mean BMIs in the 3 higher quartiles combined were 22.9 and 26.6, respectively. None of the other epinephrine or norepinephrine variables during rest or the cold pressor test were significantly related to changes in BMI, waist circumference, or triceps skinfold thickness.

In multiple regression analyses of BMI, waist circumference and triceps skinfold thickness at follow-up, the absolute epinephrine response to mental stress at entry was a consistent negative predictor for all 3 body fat variables after 18 y, after adjustment for level of exercise and entry BMI, waist circumference, and triceps skinfold thickness (**Table 3**). The norepinephrine response at entry was a weak positive predictor of future waist

Table 2

Associations between variables and epinephrine response at entry

Variable at entry	Quartiles of epinephrine response to mental stress (pg/mL)				<i>P</i> ²
	1 (11.3 ± 19.7) ¹	2 (44.0 ± 27.8)	3 (100.1 ± 54.7)	4 (146.0 ± 75.7)	
BMI (kg/m ²)	22.1 ± 3.2	22.6 ± 2.8	23.7 ± 2.6	22.5 ± 3.5	0.95
Waist circumference (cm)	80.3 ± 8.1	82.2 ± 7.2	87.0 ± 9.0	83.0 ± 13.6	0.42
Triceps skinfold thickness (mm)	10.1 ± 4.5	9.0 ± 3.2	12.9 ± 5.7	9.4 ± 4.0	0.78
Systolic blood pressure (mm Hg)	120.1 ± 14.5	120.0 ± 21.5	130.9 ± 21.5	134.0 ± 22.5	0.15
Diastolic blood pressure (mm Hg)	64.8 ± 20.7	71.1 ± 17.8	71.9 ± 14.8	73.6 ± 14.6	0.39
Heart rate (beats/min)	67.6 ± 20.7	60.1 ± 10.2	68.1 ± 11.3	61.6 ± 15.4	0.37
Total serum cholesterol (mmol/L)	4.2 ± 0.7	3.9 ± 0.7	3.9 ± 0.8	4.1 ± 0.8	0.56
Serum HDL (mmol/L)	1.1 ± 0.2	1.2 ± 0.2	1.0 ± 0.2	1.2 ± 0.2	0.81
Serum triacylglycerol (mmol/L)	0.9 ± 0.5	0.8 ± 0.3	0.9 ± 0.4	0.8 ± 0.4	0.51
Fasting plasma glucose (mmol/L)	4.1 ± 0.6	4.1 ± 0.4	4.2 ± 0.5	4.2 ± 0.5	0.65
Daily smokers [n (%)]	7 (44)	8 (53)	5 (31)	3 (19)	0.08
Epinephrine during rest (pg/mL)	67.5 ± 44.2	41.4 ± 21.4	49.6 ± 26.4	30.2 ± 16.9	<0.001
Norepinephrine during rest (pg/mL)	140.2 ± 51.9	126.8 ± 33.0	126.4 ± 41.8	89.2 ± 39.7	<0.001

¹ $\bar{x} \pm$ SD (all such values).

² Univariate Pearson correlation analyses were conducted between the various variables and epinephrine response during mental stress as a continuous variable. The *P* value for smokers was derived with a chi-square test for linear-by-linear association.

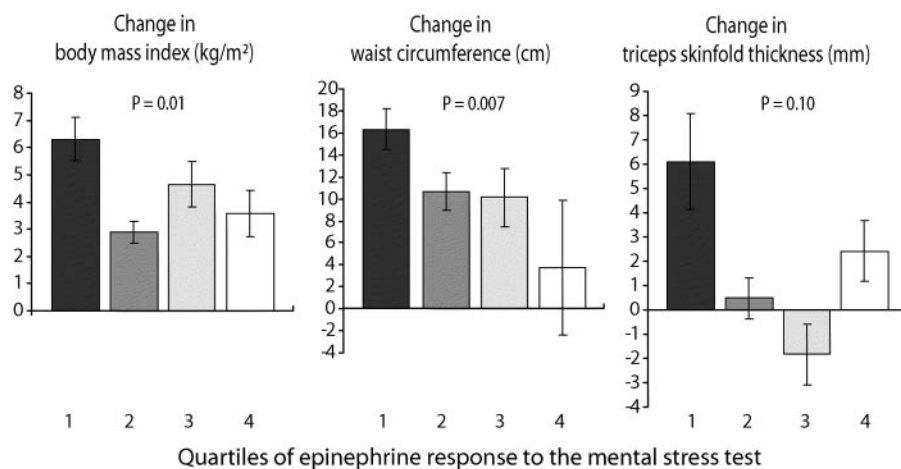


FIGURE 1. Mean (\pm SEM) changes in BMI, waist circumference, and triceps skinfold thickness over 18 y according to quartiles of epinephrine response. The mean (\pm SD) epinephrine responses were 11.3 ± 19.7 pg/mL in quartile 1, 44.0 ± 27.8 pg/mL in quartile 2, 100.1 ± 54.7 pg/mL in quartile 3, and 146.0 ± 75.7 pg/mL in quartile 4. *P* values represent Pearson correlation analyses between the change in BMI, waist circumference, and triceps skinfold thickness and epinephrine responses during mental stress as a continuous variable.

circumference and a near significant positive predictor of BMI and triceps skinfold thickness.

DISCUSSION

The present 18-y follow-up study is the first to demonstrate that reduced adrenal medullary reactivity to mental stress is related to future weight gain in whites. The epinephrine response to

mental stress was negatively related to changes in BMI and waist circumference. In supplementary multiple regression analyses, the epinephrine response was a highly consistent negative predictor of future BMI, waist, and triceps skinfold thickness after adjustment for possible confounders. The norepinephrine response to mental stress was a weak positive predictor of future waist circumference and did not significantly predict BMI and triceps skinfold thickness.

To assess sympathoadrenal activity, we measured arterial catecholamines, which were previously reported to be a more sensitive marker of overall sympathetic activity than venous sampling (19). There is uncertainty, however, about which part of the sympathetic nervous system may be the best determinant of weight development. Arterial samples reflect better the overall sympathetic activity, including spillover from heart and kidney, whereas venous samples for a larger part reflect muscle sympathetic activity. Release from muscle sympathetic nerves contributes to $\approx 50\%$ of peripheral venous norepinephrine (20). Thus, if sympathetic activity in muscle tissues is the most important determinant of future body fat, venous measurements would have been preferable and could possibly explain the weak associations between norepinephrine activity and weight development compared with epinephrine. However, there are no indications that muscle sympathetic activity is crucial in this regard. Clinically, fat tends to deposit centrally, and the sympathetic stimulation of visceral areas is better reflected through arterial sampling. In assessing the activity in the adrenal medulla, arterial sampling is far better than venous sampling because $\approx 50\%$ of epinephrine is cleared by peripheral tissues. Arterial concentrations are thus higher and more precisely determined than are venous concentrations. A limitation of the study was the lack of arterial catecholamine measurements at follow-up, because we were unable to decide whether individuals remained in the same stress quartile throughout the follow-up period.

Our main findings remained significant after adjustment for possible confounders. Heavy exercise was significantly related to both BMI and triceps skinfold thickness in the multiple regression analyses, which supports earlier findings (21). We had no information on total intake of calories or on thyroid status at

Table 3
Prediction of BMI, waist circumference, and triceps skinfold thickness¹

	β	<i>P</i>
Prediction of BMI at follow-up ²		
Covariates		
Epinephrine response to MST	-0.296	0.005
Norepinephrine response to MST	0.186	0.08
BMI at entry	0.746	<0.001
Exercise level 1 (reference level)	—	—
Exercise level 2	-0.117	0.25
Exercise level 3	-0.331	0.002
Prediction of waist circumference at follow-up ³		
Covariates		
Epinephrine response to MST	-0.594	0.002
Norepinephrine response to MST	0.405	0.04
Waist circumference at entry	0.737	<0.001
Exercise level 1 (reference level)	—	—
Exercise level 2	-0.071	0.70
Exercise level 3	-0.257	0.20
Prediction of triceps skinfold thickness at follow-up ⁴		
Covariates		
Epinephrine response to MST	-0.353	0.02
Norepinephrine response to MST	0.259	0.08
Triceps skinfold thickness at entry	0.472	<0.001
Exercise level 1 (reference level)	—	—
Exercise level 2	-0.215	0.11
Exercise level 3	-0.334	0.02

¹ Multiple regression analyses were conducted for BMI, waist circumference, and triceps skinfold thickness at follow-up. MST, mental stress test.

² Model: adjusted $R^2 = 0.585$, $P < 0.001$.

³ Model: adjusted $R^2 = 0.555$, $P < 0.001$.

⁴ Model: adjusted $R^2 = 0.309$, $P < 0.001$.

entry. Another limitation was the moderate number of participants. This, however, was partly compensated for by a very homogeneous sample, ie, the subjects were of the same race, age, and sex, which reduced the statistical variance. Moreover, the follow-up rate was high; 81% of the subjects were reexamined after 18 y. β -Blockers may affect body weight, but inclusion of this variable in the multiple regression analyses did not alter the results, and we chose to remove the variable from the final analyses because only 3 subjects were using β -blockers.

We found that higher resting concentrations of plasma epinephrine were related to lower absolute epinephrine responses to mental stress. Even though this finding may be partly explained by a regression to the mean phenomenon and to analytic uncertainties in the low plasma epinephrine range, lower resting concentrations may “permit” an increase in epinephrine more during stress. This could have been due to insufficient rest before the stress tests in other quartiles, resulting in smaller changes during stress than expected. However, before both stress tests were conducted, there was a 30-min period of supine rest, which generally is adequate. One could also argue that lower epinephrine responses only reflect a high baseline concentration, and that it is the high baseline concentration that is the marker of importance. However, resting concentrations of the catecholamines did not turn out to be independent explanatory variables of changes in body fat, pointing to the novel finding that it is the individual’s ability to react to mental stress that is the most important determinant of a later increase in body fat.

A 3.3-y follow-up study of 44 Pima Indians concluded that 24-h urine epinephrine and norepinephrine excretion rates are negative predictors of changes in waist-to-thigh circumference ratio and body weight gain, respectively (9). Even though the epinephrine findings may agree with our data, urine catecholamine excretion rates are of limited validity as markers of sympathoadrenal activity (7) and do not reflect changes during short-term stress. In our study, we were able to determine arterial plasma catecholamine concentrations at rest and during stress separately. We found the norepinephrine response to mental stress to be a positive predictor of changes in waist circumference, which suggests an association similar to that found in a 5-y follow-up study in Japanese subjects (10).

The mental stress test induces a more pronounced epinephrine release than does the cold pressor test (22) and exerts its effects mainly through activation of β -adrenergic receptors, whereas the responses to the cold pressor test are more mediated through α -receptors (13). Our finding that none of the catecholamine variables during rest or the cold pressor test were significantly related to changes in BMI, waist, or triceps skinfold thickness supports the superiority of mental stress in predicting weight gain. This agrees with the growing amount of evidence indicating that reduced stimulation of β -adrenergic receptors plays an important role in the development of obesity. Mice lacking the β_1 -, β_2 -, and β_3 -receptors were shown to develop massive obesity on a high-fat diet compared with controls (23). Furthermore, there is evidence linking polymorphisms in β_2 -adrenergic receptors to weight gain in humans (6). Excessive calorie intake in humans is believed to be sensed by the brain, which subsequently triggers diet-induced thermogenesis, accomplished by noradrenergic sympathetic stimulation of the β -adrenergic receptors (24, 25). However, these β -adrenergic receptors can also be activated by epinephrine, and a low epinephrine response to mental stress in the laboratory, which possibly also reflects lower epinephrine

reactivity to stressful daily activities, may thus favor less β -adrenergic receptor stimulation and a lower metabolic turnover and subsequent weight gain.

Over the past 2 decades, there has been an intense debate on the relation between obesity and the sympathoadrenergic system. At the beginning of the 1990s, based on urine catecholamines in cross-sectional studies, a consensus was reached that sympathetic nervous and adrenal medullary system activities are reduced in obesity. However, more sophisticated and accurate methods, such as sympathetic nerve recording techniques and isotope dilution methods measuring norepinephrine release from sympathetic nerves, later demonstrated that human obesity, accompanied by activation of the sympathetic nervous system, was believed to be an adaptation to the increased weight (7). Our study suggests that reduced adrenal medullary activity may be one important causal factor. Increased weight gain may then trigger a subsequent activation of the sympathetic nervous system. In a setting with increased sympathetic tone, the β -responsiveness may decrease, leading to further weight gain and BP elevation (26–28).

In summary, we have presented the findings of the first long-term follow-up study of the relation between sympathoadrenal activity and future overweight and central adiposity in whites. The results indicate that epinephrine activity during mental stress is a negative predictor of BMI, waist circumference, and triceps skinfold thickness after 18 y of age. These findings will contribute to the ongoing debate concerning the relation between obesity and sympathoadrenal activity and provide further insight into the pathophysiology of obesity.

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