CLINICAL—ALIMENTARY TRACT

Quantitative Gastrointestinal and Psychological Traits Associated With Obesity and Response to Weight-Loss Therapy

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BACKGROUND & AIMS: Weight loss after pharmacotherapy varies greatly. We aimed to examine associations of quantitative gastrointestinal and psychological traits with obesity, and to validate the ability of these traits to predict responses of obese individuals to pharmacotherapy. **METHODS:** In a prospective study, we measured gastric emptying of solids and liquids, fasting and postprandial gastric volume, satiation by nutrient drink test (volume to fullness and maximal tolerated volume), satiety after an ad libitum buffet meal, gastrointestinal hormones, and psychological traits in 328 normal-weight, overweight, or obese adults. We also analyzed data from 181 previously studied adults to assess associations between a subset of traits with body mass index and waist circumference. Latent dimensions associated with overweight or obesity were appraised by principal component analyses. We performed a proof of concept, placebo-controlled trial of extended-release phentermine and topiramate in 24 patients to validate associations between quantitative traits and response to weight-loss therapy. **RESULTS:** In the prospective study, obesity was associated with fasting gastric volume ($P = .03$), accelerated gastric emptying ($P < .001$ for solids and $P = .011$ for liquids), lower postprandial levels of peptide tyrosine tyrosine ($P = .003$), and higher postprandial levels of glucagon-like peptide 1 ($P < .001$). In a combined analysis of data from all studies, obesity was associated with higher volume to fullness (n = 509; $P = .038$) and satiety with abnormal waist circumference (n = 271; $P = .016$). Principal component analysis identified latent dimensions that accounted for approximately 81% of the variation among overweight and obese subjects, including satiety or satiation (21%), gastric motility (14%), psychological factors (13%), and gastric sensorimotor factors (11%). The combination of phentermine and topiramate caused significant weight loss, slowed gastric emptying, and decreased calorie intake; weight loss in response to phentermine and topiramate was significantly associated with calorie intake at the prior satiety test. **CONCLUSIONS:** Quantitative traits are associated with high body mass index; they can distinguish obesity phenotypes and, in a proof of concept clinical trial, predicted response to pharmacotherapy for obesity. ClinicalTrials.gov Number: NCT01834404.

Obesity prevalence continues to increase worldwide[1] and, in the United States, 69% of adults are overweight or obese.[2] Despite advances in understanding of some aspects of obesity pathophysiology, weight loss with current nonsurgical treatments, including diet, exercise, and medications is highly variable.[3] For example, the high dose of extended release (ER) phentermine-topiramate, a recently approved medication for management of obesity, was associated with a mean weight loss of 9.8%; however, only 48% of patients lost >10% of their body weight, and 30% of patients lost <5% of their body weight.[4]

Little is known about quantitative traits that predispose to weight gain and predict weight loss in response to nonsurgical therapy.[5] Previous retrospective studies have identified specific individual demographic factors were independent predictors of successful weight loss. For example, older age, race, older age when first overweight, fewer self-implemented weight-loss attempts, greater exercise self-efficacy, greater dietary restraint, fewer fat-related dietary behaviors, and more sedentary activity level were independent predictors of successful weight loss in the Diabetes Prevention Program,[6] the STORM trial (Sibutramine Trial of Obesity Reduction and Maintenance),[7] and the Weight Loss Maintenance Trial.[8] Additionally, psychological and behavioral variables have been used to predict successful weight loss in women.[9,10] However, the predictors of clinically relevant weight loss with currently available obesity pharmacotherapy are unclear after the withdrawal of sibutramine.

The gastrointestinal tract is essential in the regulation of food intake, a key component of energy balance. The gastrointestinal system is the site of origin of satiation and satiety signals, which communicate and interact with the brain and other organs involved in energy homeostasis. The control of food intake (ie, meal size and frequency of meals) is a major factor in the determination of the individual's weight status.[11] The most simplistic equation of obesity is based on the imbalance between caloric intake and insufficient energy expenditure. Despite the assumption that increased food intake results in higher body weight and/or body mass index (BMI), this has not been demonstrated in a controlled environment, such as the laboratory setting. This lack of correlation between food intake and body weight is attributed to behavioral inhibition of food intake by obese individuals in a testing environment.[12] Therefore, it is still necessary to prove that individuals with higher BMI consume more calories and to appraise quantitative physiological and psychological factors that account for any discriminant factors.

Gastrointestinal functions, such as gastric emptying (GE) and gastric volume (GV), influence food intake[13] and they can therefore influence body weight. However, studies of GE in obesity have shown highly divergent or contradictory results. The vast majority of earlier studies of gastrointestinal functions involved small cohorts[14,15] and used poorly validated methods.[16] In an earlier study in 48 overweight or obese patients, we reported that obesity is associated with either normal[17] or, paradoxically, lower postprandial GV measured by noninvasive imaging (single photon emission computed tomography) and lower maximal tolerated volume in a satiation test.[18] On the other hand, bulimic patients have greater GV.[19] Among psychological traits, higher anxiety and depression scores are associated with less weight loss after lifestyle modification programs.[20] Given these contradictory results on the associations of gastric functions with higher BMI in the published literature, it is essential to study a large and representative cohort of overweight and obese individuals, and also to appraise the potential association with psychological traits. In addition, because abdominal obesity, as defined by an abnormal waist circumference, is associated with metabolic syndrome and diabetes independently of body weight and BMI,[21] we also appraised the quantitative gastrointestinal traits relative to waist circumference.

Our hypotheses were (1) that there are definable phenotypes of obesity based on quantitative gastrointestinal physiological and psychological or behavioral traits and (2) physiological traits predict short-term weight-loss response to pharmacotherapy in obesity. Our aims were to examine the association of quantitative gastrointestinal and psychological traits with BMI and waist circumference; to identify latent dimensions in obesity; and to validate the use of quantitative traits in predicting response to a specific pharmacotherapeutic agent approved for treatment of obesity.

Materials and Methods

Study Design

Our study involved 3 cohorts comprising 509 predominantly (91%) Caucasian adults of normal weight, overweight, or obese (based on World Health Organization classification). We measured gastrointestinal and psychological traits in a prospectively studied cohort of 328 adults (cohort 1). In addition, we incorporated a databank of 181 normal-weight, overweight, or obese adults who had previously undergone the same measurements before any intervention using the same methods in our laboratory (cohort 2).[18,22–29] We assessed the association of the gastrointestinal and psychological traits with BMI and waist circumference. Latent dimensions were sought using principal component analysis in 231 participants in whom all the quantitative and psychological traits were prospectively collected. The third cohort consisted of 24 patients (randomly selected from the prospective cohort) who consented to participate in a randomized, placebo-controlled trial of the effects of phentermine-topiramate-ER on weight loss and quantitative traits. These data also served to appraise the ability of 5 pre-selected quantitative traits to predict weight loss in response to phentermine-topiramate-ER.

All protocols were approved by the Mayo Clinic Institutional Review Board, and research authorization to use data from the medical record was checked for all participants.

Participants

The entire study cohort consisted of 509 adults of normal weight (BMI 18–24.9 kg/m^2; n = 85), overweight (BMI 25–29.9 kg/m^2; n = 158), obesity class I (BMI 30–34.9 kg/m^2; n = 135), or obesity class II or III (BMI $\geq$35 kg/m^2; n = 131). The waist circumference was classified as normal (women <88 cm and men <102 cm) or abnormal (based on World Health Organization classification). Anthropometric measurements were done during the screening visit in the morning, in a nonfasting state. Waist and hip circumferences at the end of normal expiration were obtained by trained physicians following World Health Organization guidelines.[30] All participants were recruited by public advertisement as described elsewhere.[18] The main inclusion criteria were men or women with BMI >18 kg/m^2, age 18 years or older, and not on current treatment for other diseases other than hypothyroidism. Exclusion criteria were a positive history of any systemic disease, concurrent treatment of gastrointestinal motility or psychological disorders (ie, eating disorder, anxiety, depression) or weight-loss medications. Permitted medications were stable doses (for at least 30 days before the studies) of birth control pills, estrogen, and L-thyroxine replacement. Women of childbearing potential had a negative pregnancy test within 48 hours of any test involving radioisotopes.

Quantitative Gastrointestinal, Behavioral, and Psychological Traits

On different days, participants attended the Mayo Clinic Clinical Research Unit at 7:00 AM after an 8-hour fasting period, and the following validated quantitative traits were performed as in earlier studies: GE of solids and liquids by scintigraphy[18]; fasting and postprandial GV by a validated single photon emission computed tomography[31–33]; satiation by nutrient drink test with Ensure (Abbott Laboratories, Abbott Park, IL)[34]; satiety by ad libitum buffet meal to measure total caloric intake and macronutrient distribution in the chosen food[18]; and selected plasma gastrointestinal hormones.[18] These methods are described in detail in the Supplementary Material.

Details on self-administered questionnaires assessing affect, exercise performance, attitudes, satisfaction with body image, and eating behavior[35–39] are found in the Supplementary Material.

These psychological and behavioral traits were assessed by Hospital Anxiety and Depression Inventory,[35] AUDIT-C Alcoholism Screening Test,[39] Questionnaire on Eating and Weight Patterns-Revised,[38] the Multidimensional Body-Self Relations Questionnaire,[36] the Physical Activity Stages of Change Questionnaire,[40] and the Weight Efficacy Life-Style Questionnaire.[41] Each participant completed a series of validated questionnaires during their screening visit and, after informed consent was signed, two participants had high anxiety levels at the screening visit, and their quantitative measurements were postponed until their anxiety levels on the Hospital Anxiety and Depression Scale had improved. Ten participants were excluded from the study based on responses to the questionnaires on "Eating and Weight Patterns-Revised" and "Eating Behaviors," which suggested possible eating disorders.

Randomized, Placebo-Controlled Trial of Phentermine-Topiramate Extended Release

From the prospective cohort of approximately 270 patients, the first 24 obese (BMI 30–40 kg/m^2) adults who volunteered by responding to an invitation to participate in a therapeutic study were randomized in a parallel-group, double-blinded, 2-week treatment trial of placebo compared with phentermine-topiramate-ER at doses of 3.75 mg and 23 mg, respectively, for the first 5 days, and 7.5 mg and 46 mg for the next 10 days, for a total of 15 days of combination treatment (Supplementary Figures 1 and 2). Allocation was concealed from the clinical research team; randomization was conducted by an independent Mayo statistician who was otherwise not involved in the study, and was communicated to and retained by the Study Research Pharmacist. Randomization was carried out within blocks of consecutive patients. Only the independent Mayo statistician and pharmacist knew the block size being used. The study was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines. Written informed consent was obtained from all patients before participation. The study was registered at ClinicalTrials. gov (NCT01834404).

After written informed consent and screening evaluation, participants completed questionnaires, underwent a physical examination, a baseline satiation (nutrient drink test) on day 0, and a negative urine pregnancy test 48 hours before doing tests involving radioactivity. They presented to the testing facility (Clinical Research Unit, Mayo Clinic) after overnight fast for all quantitative measurements, which were completed on separate days in the following order in the last 3 days of the approximately 12 days (+3) of medication administration: scintigraphic GE, satiation, and single photon emission computed tomography/satiety test.

Post-treatment weight was not available in one subject (who had been randomized to placebo), and therefore an intention-to-treat analysis was performed imputing a value for "weight change" in this individual, based on the mean weight change in the remaining subjects with complete data (n = 23).

Based on primary response measures and coefficient of variation,[29,31,42,43] we estimated that with 12 patients per treatment arm, the mean effect size detectable (with 80% power based on a 2-sample t test at a 2-sided α level of .05) for GE T$_{1/2}$ was 46 minutes, satiation (maximum tolerated volume) 439 mL, fasting GV 92 mL and postprandial GV 93 mL.

Statistical Analysis

We analyzed the association of BMI class with quantitative traits using 1-way analysis of variance models pairwise comparisons of quantitative traits in overweight, obesity class I and class II/III vs normal weight were examined using Dunnett test. Associations with waist circumference were assessed using the rank sum test. The primary end points in Table 1 are parameters that reflect discrete physiological or psychological traits, therefore, no adjustment of the P values was done for multiple tests among these end points, except for the 2 satiation end points (adjusted based on the Hochberg method[44]).

A principal component analysis was examined to identify possible latent dimensions in 231 patients who had prospectively completed all quantitative and psychological traits measured. A rank transformation was used to compensate for several quantitative traits with non-normal distributions. Interpretations of the first 7 principal components (accounting for approximately 81% of the variation among the quantitative traits) were assessed based on univariate associations using Spearman correlations. Significant associations were identified based on $r_s \geq 0.4$ and $P < .0001$. The principal component analyses were constructed to be uncorrelated with age and BMI.

Effects of phentermine-topiramate-ER on weight loss and quantitative traits were assessed using analysis of covariance adjusting for baseline satiation (volume to fullness and maximum tolerated volume), BMI, or sex as covariates, depending on the specific quantitative trait.

In all statistical analyses, suitable transformations for skewness in the distributions of the measured responses or uneven variation were made as necessary.

Finally, we assessed potential differential treatment effects based on 5 prespecified quantitative traits measured within 2 years of the treatment trial (satiety by buffet meal, satiation by volume to fullness, GE of solids, fasting GV, and peak plasma PYY). This was achieved by incorporating interaction terms for treatment by quantitative trait in separate analysis of covariance models.

The authors had access to the study data and reviewed and approved the final manuscript.

Results

Association of Body Mass Index With Quantitative Traits

In the entire cohort of 509 participants (mean ± SD age 37.5 ± 12.2 years; 67.2% females; 91% Caucasians of normal weight, n = 85; overweight, n = 158; obesity class I, n = 135; or obesity class II, n = 131), obesity was associated with decreased satiation measured by a higher volume to reach fullness ($P = .038$), but not maximal tolerated volume ($P = .38$) (Table 1) on the nutrient drink test.

In the 328 prospectively studied participants (age 37.8 ± 12 years; 67.7% females; normal weight, n = 22;

Table 1. Quantitative Traits of Satiation, Gastric Motor Functions, and Gastrointestinal Hormones in Normal-Weight, Overweight, and Obese Patients

	BMI group				
Quantitative traits	Normal weight (BMI 18–25 kg/m²)	Overweight (BMI 25–30 kg/m²)	Obesity class I (BMI 30–35 kg/m²)	Obesity class II/III (BMI >35 kg/m²)	P value
Satiation test					
n (total n = 509)	85	158	135	131	
Sex, female, %	71	61	67	75	.032
BMI, kg/m²	22.8 ± 0.2	27.6 ± 0.1	32.4 ± 0.1	38.9 ± 0.3	
Volume to fullness, mL	666.4 ± 32.4	713.5 ± 20.3	755.1 ± 30.9	805.2 ± 36.9[a]	.038[b]
MTV, mL	1248 ± 42	1337 ± 30	1283 ± 34	1290 ± 39	.38[b]
Gastric motor functions and gastrointestinal hormones					
n (total n = 328)	22	105	108	93	
Age, y	38.8 ± 3.1	37.3 ± 1.2	38 ± 1.2	37.5 ± 1.2	
Sex, female, %	64	60	73	70	.20
Mean BMI, kg/m²	23 ± 0.3	27.8 ± 0.1	32.3 ± 0.1	38.9 ± 0.3	
Solid GE $T_{1/2}$, min	124.2 ± 4.1	100.2 ± 2.5[a]	99.4 ± 2.5[a]	106.6 ± 3.3[a]	<.001
Liquid GE $T_{1/2}$, min	27.9 ± 3.4	18.5 ± 0.1[a]	18.9 ± 1[a]	20 ± 1.4[a]	.011[c]
Fasting GV, mL	257.5 ± 14.5	251.7 ± 7	264.7 ± 6.3	282.2 ± 8.2	.028
Postprandial GV, mL	781.1 ± 21.5	733.6 ± 11.2	739.8 ± 11.2	767 ± 13.9	.109
Buffet meal intake, kcal	NA	948.1 ± 31.9	972.7 ± 30.7	987.5 ± 32.1	.66
Ghrelin fasting, pg/mL	NA	85.2 ± 7.2	69.5 ± 3.6	70.14 ± 6.7	.063[c]
CCK peak, pmol/L	NA	8.3 ± 0.6	8.4 ± 0.5	10.5 ± 0.8	.061[c]
GLP-1 peak, pM	12.1 ± 1.9	17.7 ± 1.1[a]	18.8 ± 1.2[a]	19.1 ± 1.3[a]	<.001[c]
PYY peak, pg/mL	223.1 ± 22.5	155.8 ± 5.9[a]	165.5 ± 9.7[a]	166.8 ± 7.9	.003[c]
Psychological traits					
Anxiety (scale 0–14)	NA	2.7 ± 0.2	4.0 ± 0.3	3.7 ± 0.3	.006[c]
Depression (scale 0–14)	NA	1.2 ± 0.2	1.8 ± 0.2	1.7 ± 0.2	.017[c]
Body image (scale 9–45)	NA	30.7 ± 0.7	27.1 ± 0.6	26.1 ± 0.6	<.001

NOTE. Data are mean ± SEM unless otherwise indicated.
CCK, cholecystokinin; MTV, maximum tolerated volume; NA, not assessed.
[a]$P < .05$ when compared with normal weight (Dunnett test).
[b]Adjusted for two end points (Hochberg method).
[c]Based on a rank transformation.

overweight, n = 105; obese class I, n = 108; and obese class II, n = 93), obesity was associated with higher fasting GV ($P = .03$), accelerated GE $T_{1/2}$ for solids ($P < .001$) and liquids ($P = .011$).

In the overweight and obese groups, there were associations of BMI with lower peak postprandial PYY ($P = .003$), higher peak postprandial glucagon like peptide-1 (GLP-1) ($P < .001$), borderline lower fasting ghrelin ($P = .063$), and borderline higher peak postprandial cholecystokinin ($P = .061$) levels. There was no association of BMI with kilocalorie intake at the buffet meal satiety test (Table 1).

Association of Abnormal Body Mass Index With Behavioral and Psychological Traits

In 274 participants (age 37.4 ± 11.8 years; 69.5% females; overweight, n = 90; and obese, n = 184), 62% of obese individuals reported exercising regularly compared with 80% of overweight individuals ($P = .004$, Supplementary Table 1). In addition, obesity was associated with higher anxiety ($P = .006$) and depression ($P = .017$) scores, and with lower body image satisfaction ($P < .001$) when compared with the overweight group (Table 1).

Association of Waist Circumference With Quantitative Traits

In 264 participants (age 37.4 ± 11.8 years; 69.5% females; normal waist circumference, n = 59; and abnormal waist circumference, n = 205), there were associations with age ($P = .08$) and, as expected, with BMI ($P < .001$). Abnormal waist circumference was associated with increased caloric intake at the ad libitum buffet meal test ($P = .016$) (Table 2), manifested as increased intake for all macronutrients (carbohydrates; $P = .06$; protein, $P = .008$; and fat, $P = .004$) compared with those with normal waist circumference. Abnormal waist circumference was not associated with GE, GV, satiation, or gastrointestinal hormones.

Association of Waist Circumference With Behavioral and Psychological Traits

Among the 264 overweight or obese participants, 64% of obese individuals reported exercising regularly compared with 83% of overweight individuals ($P = .005$) (Supplementary Table 2). Abnormal waist circumference was associated with increased depression score ($P = .038$) and lower body image satisfaction ($P < .001$), but not with

Table 2. Quantitative Traits of Satiation, Gastric Motor Functions, and Gastrointestinal Hormones Based on Waist Circumference in Both Sexes

Quantitative traits	Normal WC[a]	Abnormal WC	P value[b]
Demographics			
n (total n = 264)	59	205	
Age, y	35.3 ± 1.7	37.9 ± 0.8	.08
Sex, female, %	49	75	<.001
BMI, kg/m^2	28.02 ± 0.2	34.5 ± 0.3	<.001
Waist circumference, cm	87.9 ± 1	104.9 ± 0.7	
Satiation/satiety			
Volume to fullness, mL	664.7 ± 32.8	723.3 ± 24.1	.22
MTV, mL	1240 ± 47.9	1303 ± 30.7	.45
Buffet meal intake, kcal	893.5 ± 32.9	992.7 ± 21.6	.016
CHO intake at buffet meal, kcal	476 ± 16.8	525.2 ± 12.0	.06
Protein intake at buffet meal, kcal	200.8 ± 7.6	225.6 ± 4.8	.008
Fat intake at buffet meal, kcal	204.3 ± 9	236.7 ± 5.4	.004
Gastric motor functions and gastrointestinal hormones			
Solid GE $T_{1/2}$, min	99.7 ± 3.5	99.7 ± 1.9	.76
Liquid GE $T_{1/2}$, min	18.2 ± 1.4	19 ± 0.7	.39
Fasting GV, mL	273.3 ± 9.9	274.6 ± 5.3	.84
Postprandial GV, mL	753.4 ± 16.4	754.1 ± 8.7	.97
Ghrelin fasting, pg/mL	70.7 ± 5.6	73.18 ± 3.6	.72
CCK peak, pmol/L	8.2 ± 0.7	9.3 ± 0.4	.13
GLP-1 peak, pM	16.2 ± 0.9	19.1 ± 0.9	.22
PYY peak, pg/mL	148.9 ± 6.5	167.4 ± 5.8	.25
Psychological traits			
Anxiety (scale 0–14)	2.9 ± 0.3	3.6 ± 0.2	.12
Depression (scale 0–14)	1.2 ± 0.2	1.7 ± 0.1	.038
Body Image Satisfaction (scale 9–45)	30.8 ± 0.8	27.2 ± 0.4	<.001

NOTE. Data are mean ± SEM unless otherwise indicated.
CCK, cholecystokinin; CHO, carbohydrates; MTV, maximum tolerated volume; WC, waist circumference.
[a]Normal waist circumference is based on <102 cm for men and 88 cm for women.
[b]Based on rank sum test.

anxiety score (Table 2) when compared with those with normal waist.

Latent Dimensions of Obesity Based on Principal Components Analysis

The principal component analysis identified 4 main latent dimensions (each with $r_s > 0.4$, $P < .0001$) accounting together for approximately 81% of the variation in the rank scales of the traits among overweight and obese subjects: satiety (kilocalories at buffet meal, satiation volume to fullness and maximal tolerated volume, peak postprandial GLP-1 and PYY [21%]); gastric capacity (fasting and postprandial GVs [14%]); psychological (anxiety, depression, body image satisfaction [13%]); gastric motor and sensory functions (postprandial symptoms after liquid nutrient drink test, GE,

peak postprandial PYY levels [11%]) (Table 3). In addition, separate contributions to the overall variation were identified for principal component analyses reflecting peak postprandial GLP-1 levels (9%), symptoms 30 minutes post satiation (6%), and body image satisfaction (6%).

Effects of Phentermine-Topiramate Extended Release on Weight Loss and Quantitative Traits

The 2 treatment groups were balanced for age, sex, and BMI (Table 4 and Supplementary Table 3). After 2 weeks of treatment, patients on phentermine-topiramate-ER lost 1.42 ± 0.4 kg when compared with patients on placebo who lost 0.23 ± 0.4 kg ($P = .03$, based on least square mean analysis, adjusted for sex). There were no adverse effects reported in either treatment group.

Phentermine-topiramate-ER resulted in a decrease in caloric intake (mean difference [Δ] 206 kcal; $P = .032$) when compared with the placebo group in the satiety test. Active treatment group also had borderline significant delay in GE $T_{1/2}$ (Δ 19 minutes; $P = .057$), and percent of the meal emptied at 2 hours (mean Δ relative to placebo 10%; $P = .052$) and 4 hours (mean Δ relative to placebo 6%; $P = .030$). There were no effects of treatment on fasting and postprandial GV, satiation, liquid GE, or gastrointestinal hormones (ghrelin, cholecystokinin, GLP-1, and PYY).

Quantitative Traits as Predictors of Response to Phentermine-Topiramate Extended Release

Among the 5 prespecified traits, we noted that satiety by ad libitum buffet meal conducted in the same participants before the proof-of-concept treatment trial was significantly correlated with the post-treatment satiety test result for all subjects ($r = 0.76$; $P < .001$) and in each intervention group: phentermine-topiramate ER ($r = 0.60$; $P = .04$) and placebo ($r = 0.92$; $P < .001$) groups (Figure 1, upper panel). A differential effect of phentermine-topiramate-ER on weight loss was identified ($P = .029$) with higher kilocalorie intake at the earlier satiety test, predisposing to greater weight loss in the active treatment group (Figure 1, lower panel).

There were no differential treatment effects on weight change associated with solid GE $T_{1/2}$, fasting GV, volume to fullness (satiation), and peak postprandial PYY.

Discussion

Quantitative traits of gastric function and satiation, as well as behavioral traits, are associated with higher BMI compared with normal BMI. These traits identify distinct obesity phenotypes, and a simple measurement of satiety predicts short-term response to obesity pharmacotherapy.

Our findings suggest that, compared with normal-weight controls, those who are overweight or obese have significant differences in gastrointestinal quantitative traits: lower satiation manifested as higher Ensure volume intake to feel fullness; accelerated GE of liquids and solids; increased fasting GV; and decreased peak postprandial serum PYY. In addition, we noted higher caloric intake to record satiety in

Table 3. Latent Dimensions of Quantitative Traits Identified in Association With Obesity Based on $r \geq 0.4$ and $P < .0001$, Using Principal Components Analysis

Quantitative trait	Principal component			
	1	2	3	4
LD	Satiety/satiation	Gastric capacity	Psychological	Gastric motor/sensory
Satiety (kcal intake)	0.67			
Satiation (volume to fullness)	0.74			
Satiation (MTV)	0.80			
Satiation symptoms				0.61
Solid GE $T_{1/2}$	−0.46			0.53
Fasting gastric volume		0.83		
Postprandial Δ gastric volume		−0.81		
Postprandial peak GLP-1	0.40			
Postprandial peak PYY	0.51			0.42
HADS Anxiety			0.77	
HADS Depression			0.74	
Body Image Satisfaction			−0.48	
Attributable proportion of quantitative trait variance based on LD, %	21	14	13	11

HADS, Hospital Anxiety and Depression Scale; LD, latent dimension; MTV, maximum tolerated volume.

Table 4. Effects of Phentermine-Topiramate Extended Release and Placebo on Obesity and Quantitative Traits in a Proof of Concept, Randomized, Double-Blind Trial

Quantitative traits	Placebo	Phentermine-topiramate-ER	P value
Baseline measurements			
n	12	12	
Age, y	38.2 ± 2.4	31.8 ± 1.8	
BMI, kg/m^2	33.9 ± 1.9	35.8 ± 0.9	
Waist, cm	111.2 ± 2.2	108.5 ± 2.2	
Fasting plasma glucose, mg/dL	96.5 ± 3.6	94.2 ± 2.7	
Volume to fullness, mL	710 ± 95	712 ± 86	
Maximum tolerated volume, mL	1227 ± 111	1368 ± 111	
Effects of treatment			
Weight change			
Baseline weight, kg	105.1 ± 3.0	99.8 ± 3.1	
Post-treatment weight, kg	105.3 ± 3.5	98.4 ± 3.0	
Weight change, kg[a]	−0.23 ± 0.4	−1.42 ± 0.4	.03
Primary end points[a]			
Solid GE $T_{1/2}$, min	88 ± 7	109 ± 7	.057
Fasting gastric volume, mL	261 ± 25	227 ± 25	.36
Postprandial gastric volume, mL	681 ± 37	680 ± 37	.99
Volume to fullness, mL	630 ± 61.1	570 ± 63.2	.45
Maximum tolerated volume, mL	1108 ± 79	966 ± 79	.22
Buffet meal intake, $kcal$	988 ± 79	728 ± 79	.032
Secondary end points			
Solid GE: proportion emptied at 2 h[a]	0.66 ± 0.03	0.56 ± 0.03	.052
Solid GE: proportion remaining at 4 h[a]	0.16 ± 0.02	0.09 ± 0.02	.030[b]
Δ Postprandial GV (mL)[a]	420 ± 24	453 ± 24	.35
Fasting ghrelin	82.6 ± 10.8	78.1 ± 5.6	.72
Peak CCK (pg/mL)	8.3 ± 1	8.1 ± 0.9	.90
Peak GLP-1 (pg/mL)	11.9 ± 1.6	13.0 ± 1.8	.54[c]
Peak PYY (pg/mL)	166 ± 15.7	195.3 ± 21.2	.26[c]

NOTE. Data are mean ± SEM unless otherwise indicated.
CCK, cholecystokinin.
[a]Data are least square mean ± SE.
[b]Based on a rank transformation.
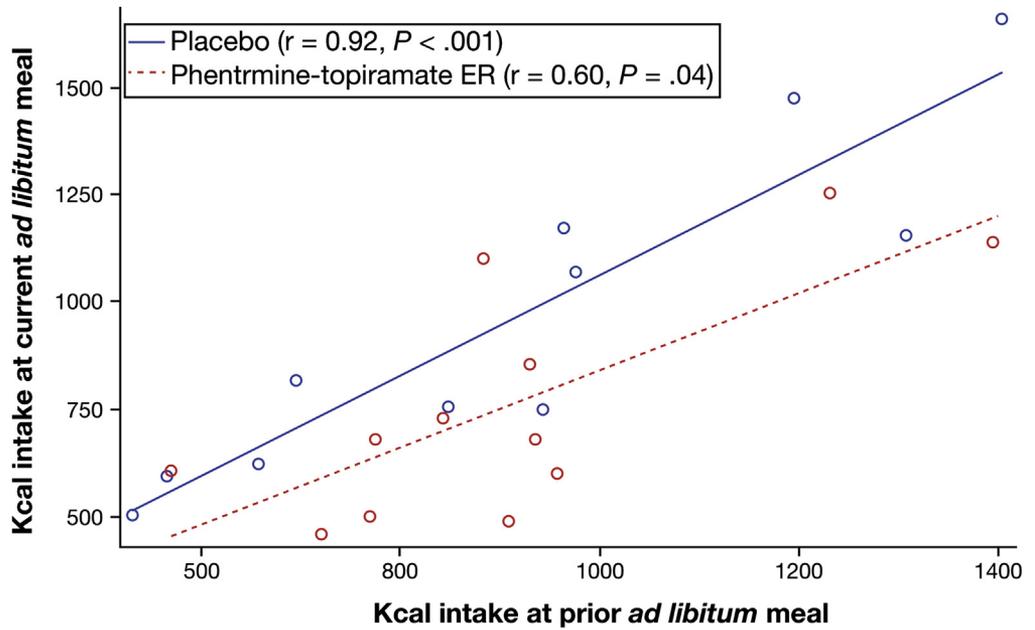[c]Rank sum test.

Figure 1. *Upper panel*: Relationship of kilocalorie intake at prior ad libitum meal and kilocalorie intake in response to randomized treatment; note that there are significant associations in both treatment groups. *Lower panel*: Association of change in body weight (in response to randomized treatment with placebo or phentermine-topiramate-ER) and kilocalorie intake at prior ad libitum meal. Note the kilocalorie intake at baseline before treatment is associated with the degree of weight loss on treatment with phentermine-topiramate-ER with no observed effect with placebo treatment. This is illustrated by $P = .029$ for the drug treatment interaction.
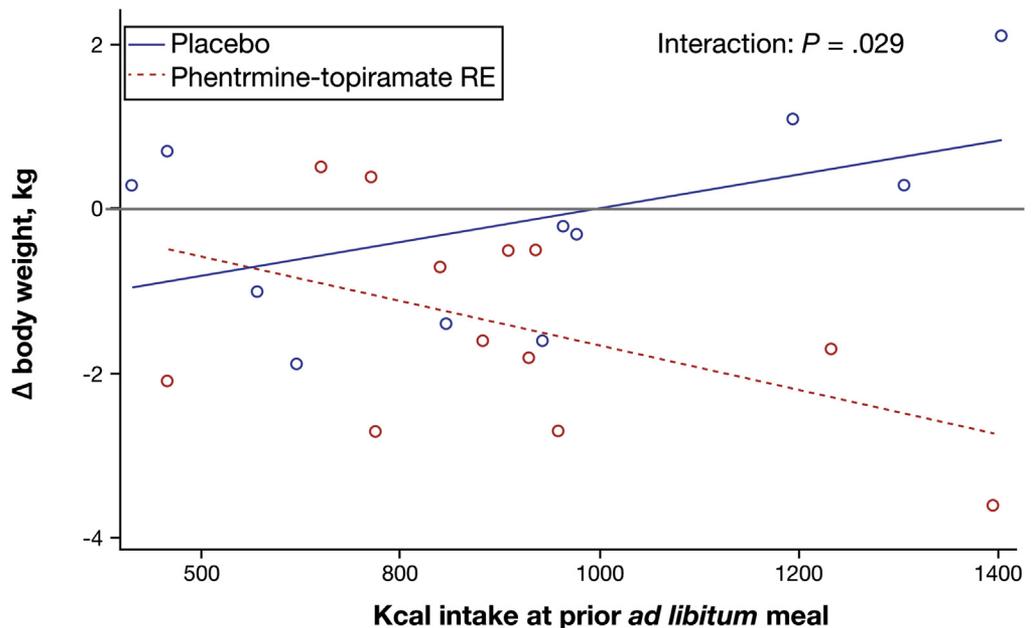
individuals with abnormal waist circumference, and there was an expected increase of peak GLP-1 in response to accelerated GE. It is interesting to note that there were also numerical trends in increasing volume to fullness, accelerating GE $T_{1/2}$, and increasing fasting GV between overweight and obesity class I and II groups. Our current data represent the largest sample of overweight or obese patients who have undergone the validated quantitative trait measurements to date. In contrast, a comprehensive review showed equivocal effects (slow, fast, or normal GE) in obesity based on multiple small studies.[14] We have previously published[45] normal value data for GE $T_{1/2}$ for 319 healthy controls for the same solid meal: 5th to 95th percentile was 78.4 to 174 minutes. Using these data, we documented that 1 of 105 in the overweight group, 1 of 108 in the class I obesity group,

and 2 of 93 in the class II/III obesity group had evidence of delayed GE at baseline. In contrast, the absolute percentages of accelerated GE of solids in these groups were 10%, 24%, and 20%, respectively.

Here we also report the first clear evidence that obesity is associated with higher caloric intake in a controlled-laboratory setting. This is associated with approximately 50 kcal higher intake per 5 kg/m^2 BMI. This numerical trend is seen also in individuals with abnormal waist circumference; individuals with abnormal waist circumference consumed 100 kcal more than the normal weight, overweight, or obese controls. With the exception of the ad libitum total calorie intake at the satiety test, abnormal waist circumference is not associated with changes in quantitative gastrointestinal traits.

The observed gastrointestinal quantitative traits in the larger patient cohort in the current study provide greater confidence in the observations of gastrointestinal dysfunction in overweight and obesity, and might explain, in part, the pathophysiology of weight gain and obesity. Therefore, individuals with higher BMI tolerated a higher caloric volume, and patients with abnormal waist circumference ingested more calories at ad libitum meal. Increased calorie intake can be facilitated by the larger fasting GV, faster GE of solids, or a decrease in the satiety hormone, PYY. Lower PYY level in obesity was reported previously.[46] Reduction of the increased fasting GV by bariatric procedures reverses the larger fasting GV and is one of the mechanisms for weight loss.[3] Our current study does not discriminate between cause and consequence of obesity, it suggests phenotypic subgroups can be identified based on pathophysiological mechanisms.

In a proof of concept, randomized clinical trial, we compared effects of phentermine-topiramate-ER and placebo on weight and quantitative traits, and explored the ability to predict weight loss based on a priori selected quantitative traits. Phentermine-topiramate-ER resulted in the expected weight loss even in a short-term (2-week) trial, slowed GE, and decreased caloric intake in a standardized satiety test. These findings suggest that phentermine-topiramate-ER has specific effects, reversing the acceleration of GE of solids, as well as reducing the calories ingested in an ad libitum meal, both traits associated with BMI. These data enhance understanding of the mechanisms of action of this drug, although the current study cannot identify which of the two medications in the combination is responsible for the pharmacodynamic effects. We have used the conventional description of phentermine-topiramate-ER as a centrally acting agent, however, the effects on stomach emptying might suggest either a peripheral action or an effect mediated through the vagal nuclei. In addition, the effect of phentermine-topiramate-ER on weight loss (which is known to be highly variable in clinical trials) is significantly associated with increased calorie intake during an ad libitum buffet meal, but not with the other gastric functions or PYY. Our findings suggest that in the short-term, obese individuals, who consume >1000 calories during ad libitum buffet meal can lose ≥1 kg per week on phentermine-topiramate ER, and the individuals on placebo had no response or actually gained weight (Figure 1, *lower panel*). This suggests that measuring satiety can facilitate prediction of efficacy during the short term. Future studies will need to appraise the prediction of the response to therapy during longer periods (12 weeks to 12 months).

In a principal component analysis conducted in 231 overweight or obese individuals and excluding the normal-weight controls because they do not have the phenotype to be predicted (ie, BMI >25 kg/m^2), we identified latent dimensions accounting together for 81% of overweight and obesity variance, including 4 main latent dimensions: satiety (21%), gastric capacity (14%), psychological (13%), and gastric motor-sensory functions (11%). These latent dimensions in obesity can serve as biomarkers to enrich selection of patients for treatment, based on the pharmacological effects of the medication. Although this principle was illustrated for the centrally acting phentermine-topiramate-ER (satiety predicted weight-loss response), it is conceivable that other biomarkers, such as rapid GE of solids in obesity, can potentially predict the response to amylin agonists, such as pramlintide, or GLP-1 agonists, such as exenatide or liraglutide, which are being tested as weight-loss remedies.[47]

Higher scores of anxiety and depression have been previously reported to be correlated with weight loss in obese patients.[20] In our cohort, obese individuals had higher anxiety and depression scores without meeting severity criteria for major depression or clinical anxiety.

In conclusion, obesity is associated with decreased satiation, accelerated GE, increased fasting GV, and decreased peak postprandial PYY, all of which can individually be associated with increased calorie intake and predispose to, or perpetuate, obesity. Our current study does not discriminate between cause or consequence of obesity, it suggests phenotypic subgroups can be identified based on pathophysiological mechanisms. Identifying a prominent phenotype, such as abnormal satiety, abnormal gastric motor function, or affect provides the opportunity to select patients for pharmacotherapeutic approaches based on the mechanisms of action of the medications. This observation has public health relevance as it would usher in a new era of matching patients based on quantitative traits to pharmacotherapy, potentially enhancing drug efficacy in treatment of obesity, and reducing expenditures for both validating the efficacy of such medications and prescribing them to obese individuals in clinical practice.

Supplementary Materials

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.11.020.

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Supplementary Materials

Quantitative Gastrointestinal Traits

1. GE of solids and liquids by scintigraphy. The primary end point was gastric half-emptying time (GE $T_{1/2}$) and secondary end points were proportion of the radiolabeled meal emptied at 2 and 4 hours.[1] Participants ingested a solid and liquid caloric meal (total calories, 296 kcal, 32% protein, 35% fat, 33% carbohydrate) in which both phases of the meal were radiolabeled: 1.0 mCi technetium-sulfur (^{99m}Tc) colloid was added to 2 raw eggs during the scrambling and cooking process. The scrambled eggs were served on one slice of buttered bread with 240 mL of 1% milk labeled with 0.1 mCi ^{111}In-DTPA. The studies were conducted as described previously.

2. Fasting and postprandial GV by a validated single photon emission computed tomography (SPECT).[2–4] We measured GV during fasting and 30 minutes after 300 mL of Ensure (316 kcal). The method has been validated previously.[5] Intravenous injection of ^{99m}Tc sodium pertechnetate, which is taken up by the parietal and non-parietal cells of the gastric mucosa, allows visualization of the stomach wall. There is high intra-observer reproducibility to measure GV with this technique.[6] The inter-individual and intra-individual coefficients of variation have been characterized[4] and there are no significant differences by sex.

   GE and SPECT studies were performed at least 72 hours apart to avoid interference by ^{111}In (indium) from the meal ingested during the GE study with the measurement of GV by ^{99m}Tc-SPECT, because ^{111}In has 2 peaks, 1 of which overlaps with the peak for ^{99m}Tc.

3. Satiation by nutrient drink test with Ensure (Abbott Laboratories; 1 kcal/mL; 11% fat, 73% carbohydrate, and 16% protein) ingested at a constant rate of 30 mL/min: during ingestion, participants recorded their sensations every 5 minutes using a numerical scale from 0 to 5, with level 0 being no symptoms, level 3 corresponding to fullness sensation after a typical meal and level 5 corresponding to the maximal tolerated volume (maximum or unbearable fullness/satiation).[7] Nutrient intake was stopped when subjects reached the score of 5. Postprandial symptoms of fullness, nausea, bloating, and pain were measured 30 minutes after the meal using 100 mm horizontal visual analog scales, with the words "none" and "worst ever" anchored at the left and right ends of the lines for each symptom.

4. Satiety by ad libitum buffet meal to measure total caloric intake and macronutrient distribution in the chosen food: this test was not performed in normal-weight participants.[1] Four hours after ingesting 300 mL liquid nutrient as part of the SPECT study, participants were invited to eat, during a 30-minute period, a standard ad libitum meal that included vegetable lasagna (Stouffers, Nestle USA, Inc, Solon, OH; nutritional analysis of each 326-g box: 420 kcal, 17 g protein [16% of energy], 38 g carbohydrate [37% of energy], and 22 g fat [47% of energy]; vanilla pudding (Hunts, Kraft Foods North America, Tarrytown, NY; nutritional analysis of each 99-g carton: 130 kcal, 1 g protein [3% of energy], 21 g carbohydrate [65% of energy], and 4.5 g fat [32% of energy]); and skim milk (nutritional analysis of each 236-mL carton: 90 kcal, 8 g protein [36% of energy], 13 g carbohydrate [64% of energy], and 0 g fat).

   The total amount (grams and kilocalories) of food consumed and the kilocalories of each macronutrient at the ad libitum meal were analyzed by using validated software (ProNutra 3.0; Viocare Technologies Inc, Princeton, NJ).

5. Plasma gastrointestinal hormones (total ghrelin, cholecystokinin, total GLP-1, and total peptide tyrosine-tyrosine [PYY]) were measured by radioimmunoassay (Linco Research, Inc.) during fasting and 15, 45, and 90 minutes postprandially,[1] with the primary end point being the peak postprandial level; ghrelin and cholecystokinin levels were not measured in normal-weight participants. Cholecystokinin was measured by EURIA assay based on an antibody with very low cross-reactivity to gastrin 17 and its sulfated counterpart, and to sensitivity to a concentration of 0.3 pmol/L.

Psychological and Behavioral Questionnaires

Each participant completed a series of validated questionnaires during their screening visit and after informed consent was signed. After signing consent, 10 participants were excluded from the study based on responses to the questionnaires on "Eating and Weight Patterns-Revised" and "Eating Behaviors" that suggest eating disorders. Two participants had high anxiety levels at the screening visit, and their testing was rescheduled until their anxiety levels on the Hospital Anxiety and Depression Scale had improved.

Hospital Anxiety and Depression Scale assessed the contribution of associated affective disorder and is based on 14 questions.[8] HADS is scored on a scale of 0–14: a score >11 points is consistent with clinical anxiety or depression and excluded the participants from the study.

AUDIT-C Alcoholism Screening Test is a 3-item alcohol screening questionnaire that reliably identifies participants who are hazardous alcohol drinkers or have active alcohol use disorders.[9] The AUDIT-C is scored on a scale of 0–12. Each AUDIT-C question has 5 answer choices. Points allotted are: a = 0 points; b = 1 point; c = 2 points; d = 3 points; e = 4 points. In men, a score of ≥4 was reviewed by study personnel. In women, a score of ≥3 was reviewed by

study personnel. When the points are all from Question #1 alone (#2 and #3 are zero), it was assumed that the patient is drinking below recommended limits and suggests that the provider review the patient's alcohol intake during the past few months to confirm accuracy. Generally, the higher the score, the more likely it is that the patient's drinking is affecting his or her safety. Participants with a score >4 were flagged to discuss the alcohol intake to confirm accuracy during the physical examination.

The Questionnaire on Eating and Weight Patterns-Revised is a valid measure of screening for eating disorders, based on a 20-item eating self-efficacy scale consisting of total score and 5 situational factors: negative emotions, availability, social pressure, physical discomfort, and positive activities.[10] Respondents are classified as binge eating disorder, purging bulimia nervosa, nonpurging bulimia nervosa, or anorexia nervosa.

After signing consent, 10 participants were excluded from the study based on abnormal questionnaire scores.

The Body Image Satisfaction–The Multidimensional Body-Self Relations Questionnaire provides a standardized attitudinal assessment of body image, normed from a national body image survey.[11] Nine items are rated on a 5-point scale, ranging from 1 (definitely disagree) to 5 (definitely agree). In this study, we used the Body Areas Satisfaction Scale, which measures feelings of satisfaction with discrete aspects of physical appearance (eg, face, weight, hair). Obese women demonstrate improvement on this scale after weight loss, and obese binge eaters score lower on this scale compared with obese individuals without an eating disorder. Therefore, the scale goes from 9 to 45.

The Eating Behaviors: The Weight Efficacy Life-Style Questionnaire is a 20-item eating self-efficacy scale consisting of total score and 5 situational factors: negative emotions, availability, social pressure, physical discomfort, and positive activities. Subjects are asked to rate their confidence about being able to successfully resist the urge to eat using a 10-point scale ranging from 0 (not confident) to 9 (very confident). Previous research has compared levels of eating self-efficacy in obese binge vs non–binge eaters.[12] We have also previously documented eating self-efficacy improvement after obesity treatment.[13]

The Physical Activity Level–The 4-item Physical Activity Stages of Change Questionnaire was used to assess the physical activity level of participants.[14] The questions were:

1. I am currently physically active;

2. I intend to become more physically active in the next 6 months;

3. I currently engage in regular physical activity; and

4. I have been regularly physically active for the past 6 months.

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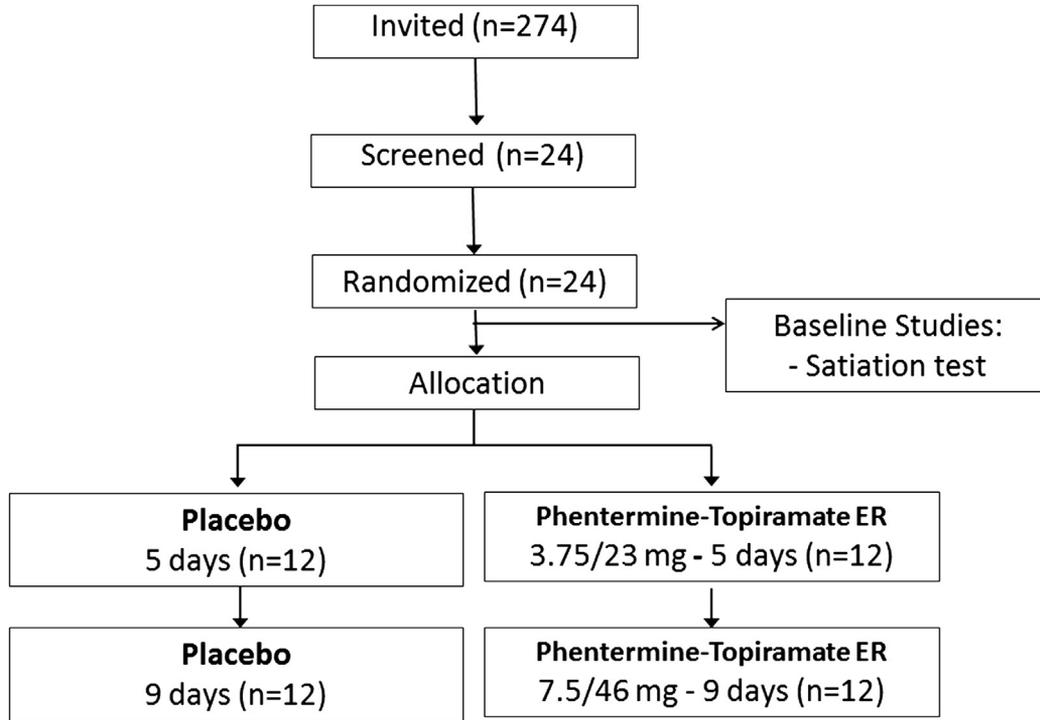
Supplementary Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow chart for randomized controlled trial of effects of phentermine-topiramate-ER on weight loss and quantitative traits in obesity.

Supplementary Figure 2. Study protocol for randomized controlled trial of effects of phentermine-topiramate-ER on weight loss and quantitative traits measured on days 12 to 14 of treatment.
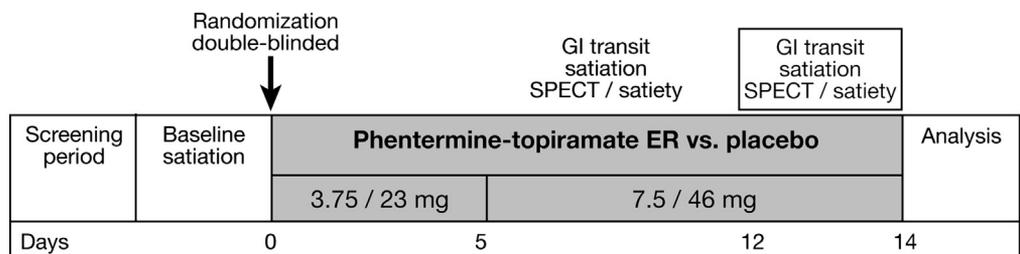
Supplementary Table 1. Exercise Behaviors and Attitudes in Overweight or Obese (Body Mass Index >30 kg/m^2) Participants

Behaviors and attitudes	Overweight	BMI ≥30 kg/m^2	P value[a]
I am currently physically active, %	81.0	61.5	.002
I intend to become more physically active in the next 6 months, %	73.0	82.32	.080
I currently engage in regular physical activity, %	65.6	44.0	.002
I have been regularly physically active for the past 6 months, %	58.9	35.4	<.001

[a]χ^2 test unless otherwise noted.

Supplementary Table 2. Exercise Behaviors and Attitudes in Overweight or Obese Participants With Normal or Abnormal Weight Circumference

Behaviors and attitudes	Normal WC	Abnormal WC	P value[a]
I am currently physically active, %	83	64	.005
I intend to become more physically active in the next 6 months, %	71	81	.11
I currently engage in regular physical activity, %	73	45	.0002
I have been regularly physically active for the past 6 months, %	62	38	.001

WC, waist circumference.
[a]χ^2 test unless otherwise noted.

Supplementary Table 3. Demographics of Participants Randomized to Placebo or Phentermine-Topiramate Extended Release

Demographics	Placebo	Phentermine-topiramate ER
Hip, *cm*	121.6 ± 4.0	116.4 ± 2.7
SBP, *mmHg*	132.7 ± 3.2	127.8 ± 3.7
DBP, *mmHg*	80.0 ± 2.7	80.4 ± 2.7
HADS Anxiety	3.2 ± 0.7	3.6 ± 0.6
HADS Depression	1.7 ± 0.6	1.6 ± 0.3
Body Image Satisfaction	28.1 ± 2.0	25.8 ± 1.7

NOTE. Data are mean ± SEM.
DBP, diastolic blood pressure; HADS, Hospital Anxiety and Depression Scale; SBP, systolic blood pressure.