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### Title

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### Permalink

<https://escholarship.org/uc/item/1th6w51w>

### Journal

Psychosomatic Medicine, 79(8)

### ISSN

0033-3174

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### Publication Date

2017-10-01

### DOI

10.1097/psy.0000000000000494

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Peer reviewed



Published in final edited form as:

*Psychosom Med.* 2017 October ; 79(8): 880–887. doi:10.1097/PSY.0000000000000494.

## Surgically induced changes in gut microbiome and hedonic eating as related to weight loss: Preliminary findings in obese women undergoing bariatric surgery

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### Abstract

**Objective**—Weight-loss surgery results in significant changes in the anatomy, function and intraluminal environment of the gastrointestinal tract affecting the gut microbiome. While bariatric surgery results in sustained weight loss, decreased appetite and hedonic eating; it is unknown if the surgery-induced alterations in gut microbiota play a role in the observed changes in hedonic eating. We explored the following hypotheses 1) Laparoscopic sleeve gastrectomy results in changes in gut microbial composition ; 2) Alterations in gut microbiota are related to weight loss; 3) Alterations in gut microbiome are associated with changes in appetite and hedonic eating.

**Methods**—Eight obese women underwent LSG. Their BMI, body fat mass, food intake, hunger, hedonic eating scores, and stool samples were obtained at baseline and 1-month post-surgery. 16S ribosomal RNA gene sequencing was performed on stool samples. DESeq2 for changes in microbial abundance. Multilevel-sparse partial least squares discriminant analysis was applied to genus level abundance for discriminative microbial signatures.

**Results**—LSG resulted in significant reductions in BMI, food intake and hedonic eating. A microbial signature comprised of 5 bacterial genera discriminated between pre and post-surgery status. Several bacterial genera were significantly associated with weight loss (*Bilophila* ( $q=3E-05$ ), *Faecalibacterium* ( $q=4E-05$ )), lower appetite (*Enterococcus*,  $q=3E-05$ ) and reduced hedonic eating (*Akkermansia*,  $q=0.037$ ) after surgery.

**Conclusions**—In this preliminary analysis, changes in gut microbial abundance discriminated between pre and postoperative status. Alterations in gut microbiome were significantly associated

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Conflict of interest: None of the listed authors have any conflict of interest

with weight loss and with reduced hedonic eating after surgery, however a larger sample is needed to confirm these findings.

### Keywords

bariatric surgery; gut microbiome; hedonic eating; sleeve gastrectomy; appetite; food addiction

## INTRODUCTION

Bariatric surgery is currently the most effective intervention for the treatment of obesity (1). The mechanisms underlying bariatric surgery-induced weight loss are complex, and are poorly understood. Implicated mechanisms include alterations in the anatomy, physiology and microenvironment of the digestive tract, which in turn result in changes in gut microbial composition and function (2–5). Remarkably, the transplantation of fecal microbiota from a post-bariatric surgery donor is able to confer weight and fat mass reduction to germ-free recipient mice (6,7). These findings support the idea that inherent properties of the post-bariatric gut microbiome are able to influence weight and metabolism. While multiple mechanisms may be involved in mediating these microbiome related effects, the possible role of changes in gut-microbiota-brain interactions affecting ingestive behaviors and hedonic eating have not been studied.

The brain-gut-microbiome axis is a bidirectional communication system which plays a central role in the maintenance of homeostasis through neuronal pathways involving the brain, the vagus and/or spinal nerves and the enteric nervous system, as well as through signaling pathways involving hormones, neuropeptides, cytokines and gut and microbe-derived metabolites. Comprehensive reviews of the brain-gut-microbiome axis structure and function are available elsewhere (8–10). There is a large body of preclinical evidence supporting a role of the gut microbiota in the regulation of anxiety, mood and appetite (11–15). In addition, fecal transplantation was able to transfer changes in eating behaviors (hyperphagia) in an animal model of metabolic syndrome (16), suggesting that the gut microbiota may also influence complex human behaviors such as hedonic eating. Increased hedonic responses to highly-palatable foods have been reported in obese individuals (17–19). Several bariatric procedures including gastric bypass (RYGB), duodenal-jejunal bypass and vertical sleeve gastrectomy have shown to decrease hedonic responses to highly-palatable foods, and to affect dopamine release in the striatum (20–23).

By assessing changes in food intake and hedonic eating after bariatric surgery and their relationship with the gut microbiome, we aimed to test the following hypotheses: 1) Laparoscopic sleeve gastrectomy (LSG) results in distinct changes in gut microbial composition that are able to discriminate between pre and post surgical status; 2) Alterations in gut microbial composition are related to weight loss and; 3) These gut microbial changes are associated with changes in ingestive behaviors that are conducive to weight loss.

## METHODS

### Study sample

Eight adult obese right-handed female subjects (age:  $39.5 \pm 8.7$  yrs, BMI:  $44.1 \pm 5.6$  kg/m<sup>2</sup>) were recruited before undergoing LSG at the UCLA Ronald Reagan Medical Center in Los Angeles, from June 2014 to June 2015. All selected subjects underwent a preoperative evaluation by a multidisciplinary team including nutritionists, bariatric surgeons, gastroenterologists, and psychologists at the Center for Obesity and Metabolic Health - COMET- following the American Gastrointestinal and Endoscopic Surgeons guidelines for bariatric surgery (24). We excluded subjects with prior major gastrointestinal surgery, history of neurological/mental disease including eating disorders, or who were using medications known to affect appetite or psychotropic medications, who were pregnant, had any contraindication for undergoing MRI, or had received antibiotics or probiotics within 3 months of inclusion. LSG was performed by one of the two bariatric surgeons (ED, YC) according to a standardized procedure. Postoperative diet progressed gradually from liquid to soft diet with a return to solid foods around 7 weeks after surgery.

The study was approved by the Biomedical Institutional Review Board at the University of California at Los Angeles (UCLA). All participants provided written consent before study participation.

### Anthropometrics and Body Composition

A certified nutritionist at the UCLA Clinical & Translational Research Center obtained measures for height, weight, BMI and waist circumference using techniques and methods described in NHANES III at baseline and at 1 month after surgery. A wall-mounted standard stadiometer (model PE-WM-60-84; Perspective Enterprises, Inc.) was used to measure standing height to the nearest 0.1 cm. An electronic scale (5002 Stand-On Scale; Scale-Tronix, Inc.) was used to obtain body weight to the nearest 0.1 kg. Body mass index (BMI) was determined by dividing weight in kg by height in meters squared. All measurements were taken in duplicate for better accuracy.

In addition, all subjects underwent a Bioelectrical impedance analysis (BIA) using a body composition analyzer (BIA Model 450 Bioimpedance Analyzer; Biodynamics, Inc.) to assess body composition using electrical tissue conductivity and provide estimates of percent body fat and lean body mass.

### Dietary Assessment

Dietary intake data were measured prospectively to obtain information about eating habits, energy, and nutrients. Subjects were provided detailed instructions to record all food and beverage consumed over a three-day period both at baseline (before surgery) and 1 month after surgery. Subject entries were reviewed for accuracy by a trained nutrition professional and entered into a nutrition analysis software (Food Processor 10.15, Esha Research) to generate a report of estimated energy and macronutrient values.

### Hunger and satiety ratings

All subjects completed two validated visual analog scales (VAS) for hunger and satiety after overnight fasting. The VAS was a 100-mm line with a phrase at each end describing the extremes. Subjects were told to make a mark across the line corresponding to their perceptions of hunger and satiety and quantification was done by measuring the distance from the left end of the scale to the mark.

### Hedonic eating assessment

All subjects filled out a questionnaires designed to measure food addiction including the Yale Food Addiction Scale (YFAS), a 25-item scale developed to measure food addiction by assessing signs of substance-dependence symptoms (e.g., tolerance, withdrawal, loss of control) in eating behavior. The YFAS has displayed a good internal reliability (Kuder–Richardson  $\alpha = .86$ ) (25). They also rated their desire to eat or “wanting” that reflects the motivational aspect of ingestive behavior. All subjects were shown pictures that depicted 4 different types of foods (high-calorie: sweets and savory food; and low calorie: fruits and salads), shown as 3 runs of each type of food and each run consisted of 4 pictures. After each run, subjects were asked to rate their experience as “how much did you want to eat what you just saw?”, on a scale from 0 to 100, zero being ‘not at all’ and 100 being ‘very much. Ratings were averaged across all runs from each condition to obtain an overall desire to eat rating for each stimuli type (high- vs. low-calorie foods; and sweets vs. savory foods vs. fruit vs. salads) for each participant, pre- and post surgery.

### Microbiome composition assessment: 16S ribosomal RNA gene sequencing

Stool samples were collected at baseline and at 1-month after surgery. The frozen fecal samples were ground with mortar and pestle in the presence of liquid nitrogen, then aliquoted. Genomic DNA was extracted using the Powersoil kit as per then manufacturer’s instructions (MoBio). The V4 region of 16S ribosomal RNA genes was amplified and underwent paired end sequencing on an Illumina HiSeq 2500 as previously described (26). The 253 base pair reads were processed using QIIME v1.9.1 with default parameters (27). Observable Taxonomic Units (OTUs) were picked against the May 2013 version of the Greengenes database, pre-filtered at 97% identity. Sequence depth ranged from 499,588 to 1,070,571.

### Diversity analysis

Alpha diversity (i.e. bacterial diversity within a sample) and beta diversity (differences in composition across samples) were calculated in QIIME v1.9.1 using data rarefied to 499,588 sequences. Alpha diversity metrics included Faith’s phylogenetic diversity metric, Chao1, and Shannon index. Pre-post surgery differences in alpha diversity were calculated using a nonparametric t-test and 1000 Monte Carlo permutations were used to calculate the nonparametric p-value. Beta diversity was calculated using unweighted and weighted UniFrac for all pairwise combinations of pre- and post-surgery samples. Adonis analysis, a permutational analysis of variance, was performed to test for differences in overall microbial composition pre- and post-surgery.

## Differences in taxonomic abundance of the gut microbiome

Differences in phylum and genus abundance between pre- and post- surgery samples were evaluated using DESeq2 in R (28). Unrarefied 16S rRNA count data were first filtered to remove OTUs present in only one sample then fitted to multivariate negative binomial models with surgery status (before and after) and subject as covariates. P-values for differential abundance between preoperative vs. postoperative status were converted to q-values to correct for multiple hypothesis testing ( $< 0.05$  for significance) (29). The significance of the Firmicutes/Bacteroidetes ratio was determined using the Mann-Whitney U test.

Multi-level sparse Partial Least Square-Discriminant Analysis (sPLS-DA) was applied to identify genus-level taxa specific able to discriminate the effects of surgery within individuals. This method accounts for repeated measurements from pre- and post- treatment assays and highlights the effect of treatment within subject separately from the biological variation between subjects (30). This projection-based technique simultaneously performs feature selection and modelling and achieves sparsity using lasso penalization (31). sPLS-DA operates using a supervised framework to find linear combinations of a limited set of variables, here genus level taxa, that *predict* pre- and post-surgery status. We refer to each linear combination or component as discriminatory “taxa signature”. sPLS-DA is our method of choice given its good classification performance and its ability to deal with a large number of predictors, small sample size, and high co-linearity among predictors (32,33). sPLS-DA was performed using the R package mixOmics (<http://www.R-project.org>).

As recommended, the number of components to identify was fixed at 1 (32,33). To select the optimal number of features for this component we estimated the leave-one-out classification error with respect to a range of number of features (5 to 200 by units of 5). This process was repeated 50 times and the results averaged. This so-called “tuning” procedure indicated that 1 component model comprised of 5 features would be optimal.

The microbial signatures were summarized using variable loadings on the components and VIP coefficients. Each selected variable has an associated “loading” indexing the relative importance of that variable in the component for group discrimination (32). Variable importance in projection (VIP) scores is a standardized measure that represents contribution of each feature relative to the variance explained by all components (33). As a rule of thumb, predictors with VIP coefficients greater than one are considered particularly important for the discrimination (32). We also use graphical displays to illustrate the discriminative abilities of the algorithms (33).

## Statistical analyses

Statistical analyses were calculated using R or SPSS version 23 (SPSS Inc., USA). The Shapiro-Wilks test was used to check for normality, and paired *t*-tests were used for changes in measures of obesity (BMI and body fat mass), appetite (fasting and postprandial hunger levels), food addiction (YFAS symptom count score, reported desire to eat high and low-calorie foods), and food intake (daily calorie intake: total, from fats, from carbohydrates and

from proteins) and measures of hedonic eating (YFAS, want to eat sweets. Associations between baseline and surgically induced changes in the clinical parameters described above and gut microbiota abundance were explored using Pearson's and Spearman's correlations, for normally distributed variables vs. non-parametric variables (bacterial genera abundance), respectively. Statistical computations were considered significant when the resulting  $p$  values were  $<0.05$ .

## RESULTS

Effects of bariatric surgery on measures of obesity, appetite and food intakeIn this sample, the mean average excess weight loss achieved at 1 month after surgery was  $27.4\pm 11.4\%$ , corresponding to a mean weight loss of 12.6 kg. LSG resulted in a marked reduction in all measures of obesity, and in measures of appetite, food intake and hedonic eating as described in Table 1. Before surgery, subjects gave higher ratings to high-calorie foods and sweet-foods than to low-calorie foods when rating their subjective desire to eat these types of foods. Baseline YFAS scores were associated with the reported desire to eat high-calorie foods ( $r=0.869$ ,  $p=0.011$ ) and displayed an even stronger but inverse correlation with the reported desire to eat low-calorie foods ( $r=-0.925$ ,  $p<0.001$ ). These associations between YFAS scores and desire to eat either high or low-calorie food were attenuated after surgery ( $r=-0.352$ ,  $p=0.393$  for high-calorie foods and  $r=-0.400$ ,  $p=0.326$  for low-calorie foods). In this sample, no associations were found between measures of food addiction and measures of appetite at baseline.

### Early effects of bariatric surgery on gut microbiota composition

To investigate the early effects of Laparoscopic Sleeve Gastrectomy on the gut microbiota, we obtained fecal samples from 6 of the subjects, 1 month before and 1 month after the procedure. These stool samples underwent sequencing of the 16S ribosomal RNA gene, a marker of bacterial taxonomy that can be used to characterize the composition of the microbiome. The significance of differences before and after surgery in taxonomic profiles at the phylum and genus levels was determined using DESeq2. This algorithm normalizes the sequence data across samples, shrinks dispersion of the count data, and fits the data to negative binomial models (one model for each taxon). The results of this analysis are expressed as a magnitude of change ( $\log_2$  fold change =  $\log_2FC$ ) and as significance ( $p$ -values are adjusted to  $q$ -values to correct for multiple hypothesis testing). LSG produced changes in the gut microbiota abundance at the phylum level, with a highly significant increase in Fusobacteria ( $\log_2FC=4.0$ ,  $q=4.1E-07$ ) and a significant reduction in the Firmicutes/Bacteroidetes ratio ( $p=0.008$ ) due to decreased Firmicutes ( $\log_2FC=-0.71$ ,  $q=0.0055$ ) after surgery (Fig. 1). There was no change in alpha diversity post-surgery. Beta diversity analysis using weighted UniFrac showed a trend towards a difference after surgery with  $p=0.056$  by Adonis. Multivariate models demonstrated differential abundance of four genera after surgery, including decreased unclassified Bifidobacteriaceae ( $\log_2FC=-8.4$ ,  $q=0.0003$ ) and increased *Fusobacterium* ( $\log_2FC=4.3$ ,  $q=0.0005$ ), *Atopobium* ( $\log_2FC=4.1$ ,  $q=0.01$ ), and *Bulleidia* ( $\log_2FC=3.8$ ,  $q=0.04$ ).



## Gut microbial signature as related to surgical status and changes in weight, and eating behaviors

Supervised learning methods were applied to identify a distinctive microbial signature comprised of 5 genus level taxa that differentiated between preoperative and postoperative status (Fig. 2). In this preliminary analysis, the signature accounted for 90% of variance in the discrimination and was comprised of 5 bacteria including *Atopobium* (Actinobacteria phylum), *Bacteroides* (Bacteroidetes), *Bulleidia* (Firmicutes), *Epulopiscium* (Firmicutes), and *TG5* (Synergistetes). The variable loadings, and their VIP coefficients for the signature are summarized in Table 2. These are measures of how much each genus contributes to differentiating pre and post-surgical status. Noticeably all members of this signature experienced a rise in their abundance after surgery.

Postoperative changes in the relative abundance of members of the microbial signature correlated with changes in clinical variables. For example, *Atopobium* was associated with changes in BMI ( $\rho=-0.943$ ,  $p=0.004$ ) and body fat mass ( $\rho=-0.828$ ,  $p=0.041$ ) and similar findings were seen for *TG5* (BMI:  $\rho=-0.885$ ,  $p=0.012$ ; body fat mass:  $\rho=-0.886$ ,  $p=0.019$ ), a genus within the Dethiosulfovibrionaceae family. Reduced desire to eat sweets post-surgery was inversely correlated with changes in the abundance of *Bulleidia* ( $\rho=-0.841$ ,  $p=0.036$ ) and *TG5* ( $\rho=-0.812$ ,  $p=0.049$ ).

## Microbial interactions with weight loss and eating behaviors

We explored whether intestinal bacterial profiles were associated with BMI, body composition (body fat mass), hunger levels and measures of food addiction (YFAS and reported desire to eat sweets) using multivariate models adjusting for subject's ID and surgical status. Twenty bacterial genera displayed at least one significant association at a rate for false discovery less than 5% ( $q<0.05$ ). Figure 3 summarizes the findings for the bacteria belonging to a known genus. Noticeably, *Enterococcus* showed a broad spectrum of associations including direct correlations with BMI ( $\log_2FC=0.13$ ,  $q=0.044$ ), body fat mass ( $\log_2FC=0.094$ ,  $q=0.034$ ) and hunger levels ( $\log_2FC=0.17$ ,  $q=3E-05$ ).

In this study, gut bacteria profiles associated with surgically induced changes in BMI and body fat mass were similar but not identical. The postoperative drop in BMI was significantly associated with 20 bacterial genera, several of them with strong inverse associations such as *Bilophila* ( $\log_2FC=-0.25$ ,  $q=3E-05$ ), *Faecalibacterium* ( $\log_2FC=-0.249$ ,  $q=4E-05$ ), *Lachnospira* ( $\log_2FC=-0.205$ ,  $q=0.003$ ), and *Acidaminococcus* ( $\log_2FC=-0.187$ ,  $q=0.003$ ). Reduction in body fat mass was related to 16 bacterial genera, with *Bilophila* again the most significant ( $\log_2FC=-0.145$ ,  $q=3E-05$ ). Hunger levels were associated with *Enterococcus* ( $\log_2FC=0.172$ ,  $q=3E-05$ ), *Odoribacter* ( $\log_2FC=0.125$ ,  $q=0.044$ ), and *Anaerostipes* ( $\log_2FC=-0.112$ ,  $q=0.051$ ). Gut microbial profiles were also associated with hedonic eating behaviors as shown in Figure 3.

## DISCUSSION

The main findings of this preliminary analysis were: 1) Laparoscopic Sleeve Gastrectomy results in distinct changes in gut microbiota composition which were able to discriminate



between the pre- and post-surgery state. 2) Surgically induced alterations in gut microbial profiles were related to weight loss and reductions in body fat mass. 3) Gut microbial profiles were associated with surgically induced reductions in appetite and in food addiction measures.

### Effect of sleeve gastrectomy on microbial signatures

Consistent with published data, we did not find large changes in diversity of the gut microbiota one month after sleeve gastrectomy, suggesting less dramatic alteration of the gut microbiome by sleeve gastrectomy, possibly related to the limited anatomical derangement of the GI tract when compared to gastric bypass (34,35). Remarkably, by using supervised machine learning methods we were able to identify a group of bacteria which changes in relative abundance discriminated between the pre and post-surgery status. This microbial signature was comprised of *Bacteroides*, *Atopobium*, *TG5*, *Bulleidia* and *Epulopiscium*, all of which bloomed after LSG. It remains to be determined if this microbial signature is sustained over time and whether it is the result of adaptive changes to the “new anatomy”, or a response to postoperative changes in diet. Several members of the *Bacteroides* genus are highly adapted to live in the colonic mucus layer. This characteristic confers them resilience and stability within the gut microbiome by adaptively directing its glycan-foraging behavior to the mucus when dietary sources of polysaccharide are scarce (36–38). It is possible, that the observed prominence of *Bacteroides* after surgery reflects changes in diet and a decreased availability of intraluminal nutrients. The other members of the signature were either not present or present at very low counts before surgery; little information about their role in obesity and/or weight loss is available. Sulfate-reducing bacteria, such as *Desulfovibrio spp.*, are important in the utilization of mucin as substrate by other bacteria. Glycan-foraging bacteria, such as *Bacteroides*, release sulfate during mucin degradation, enabling sulfate reducing bacteria to compete for H<sub>2</sub> or organic compounds, like lactate, as electron donors for reduction of sulfate (36,38–40). Thus, the postoperative bloom in *Bacteroides* and *TG5* (a member of the *Dethiosulfovibrionaceae* family) may be an indication of a mutualistic relationship between these two members of the gut microbiome.

### Role of the gut microbiota in the effect of Sleeve Gastrectomy on hunger

Fasting hunger levels were rapidly and dramatically reduced by sleeve gastrectomy, and this reduction was strongly associated with *Enterococcus*, a lactobacillus known to ferment dietary fiber producing short-chain-fatty acids (SCFA). In an animal model of diet induced obesity, fiber supplementation resulted in a bloom of *Enterococcus* and *Bifidobacterium*, an increased production of SCFA, decreased body weight gain and fat deposition, and changes in neuronal activation at the hypothalamus suggesting a satiated state (15,16). *Akkermansia*, which was weakly associated with decreased appetite in the present study, has been linked to activation of the endocannabinoid system which in turn stimulates the secretion of GLP-1 by the intestinal L-cells and reduces ghrelin levels (16,41,42).

### Role of the gut microbiota in the effect of Sleeve Gastrectomy on food preferences

To our knowledge, this is the first study to explore whether the gut microbiota play a role in the changes in food preferences seen in humans after bariatric surgery. In this small sample, we found that ratings for hedonic eating decreased after LSG and that the change was

associated with alterations of the gut microbiome. While subjects showed a preference for high-calorie foods over low-calorie foods at baseline, this preference was lost after surgery. These results parallel changes in high-hedonic value food preferences seen after RYGB, the most commonly studied bariatric procedure (21,43,44). In both preclinical and human studies, RYGB is characterized by a decreased response to food cues in brain regions of the reward system and a decrease in the palatability of highly-hedonic foods (21–23). However, the mechanisms behind surgery-related changes in hedonic eating are still elusive. Gastric bypass and sleeve gastrectomy result in an incretin profile that is “anorexinogenic” and thought to contribute in the postoperative drop in hedonic eating; however changes in hedonic eating have been shown to be independent from plasma levels of incretins or bile acids, symptoms of dumping syndrome and hunger levels (21,43,45). On the other hand, taste receptors, in the mouth and in the gut, have been implicated in appetite control, taste preferences and intake of preferred foods (43,46). For example, in an animal model with preference for sweets, the surgical diversion of the duodenum caused a decrease in dopamine release at the striatum and in the amount of sweet solution consumed by the mice (24). Authors speculated that these findings were related to bypassing sweet-receptors present in the small bowel (24). However, this theory will not apply to changes in hedonic eating seen after LSG since this procedure preserves the continuity of the GI tract. But, expression and function of sweet receptors in the gut is modulated by gut microbiota; moreover germ-free animals display an exaggerated preference for high-sucrose solutions (47). Along this, the present study found that the decline in preference for sweets after LSG was associated with alterations in the gut microbiome; specifically the *Akkermansia* genu, was significantly but inversely associated with the postoperative drop in the reported desire to eat sweets. The mechanism behind this alteration in hedonic eating is unclear and studies in larger samples should be conducted to confirm these findings. Of note, a study in rodents with high and low preference for saccharin consumption phenotypes, showed differential gut microbial composition independently of the saccharin intake suggesting a diet-independent interaction between scaccharin preference and gut microbiome (48).

This study shows that sleeve gastrectomy results in a significant reduction in scores of another measure of hedonic eating, the Yale Food Addiction scale. The postoperative drop in food addiction scores was directly associated with members of the gut microbial community including *Catenibacterium* and *Anaerostipes* and inverse correlations with *Butyricimonas*, *Enterococcus* and *Odoribacter*. Of note, alterations in abundance of metabolically active genera including, amongst others, *Enterococcus*, *Akkermansia* and *Odoribacter* have been associated with autistic behaviors in children (49). Whether or not the effect of the identified bacteria on food addiction measures is mediated by microbial production of metabolites or neuroactive substances remains to be tested. Our findings merit further assessment to confirm them in a larger sample and to try to elucidate the mechanisms behind the associations with hedonic eating.

### **Interactions between gut microbiome, sleeve gastrectomy and weight loss**

Results showed a strong inverse correlations between BMI and fat mass with a group of microbes. The most significant association was with *Bilophila*, a sulfate-reducing-bacteria which blooms in response to increased bile acid secretion induced by diets rich in animal

fats and in saturated fats from milk (50,51). *Bilophila*, as a sulfate-reducing-bacteria, produces hydrogen sulfide which has been associated with inflammatory bowel disease and disruptions in immune regulation (51, 52). The inverse correlation with weight loss measures seen in the present study may be indicative of changes in diet during the postoperative period which led to a significant drop in the consumption of fats. Other genera negatively associated with changes in BMI and fat mass include *Faecalibacterium*, *Lachnospira*, and *Acidaminococcus*. *Lachnospira* and *Faecalibacterium* have been associated with complications of obesity, including metabolic syndrome and diabetes and decrease in their abundance after RYGB correlated with a reduction in inflammatory markers (35,53).

An alternative or complementary explanation of the interaction between gut microbiome and the effect of bariatric surgery on weight and on remodeling of the body fat mass is the association between white fat tissue (WAT) genes and gut microbiome. In an animal model of RYGB, significant associations were found between several WAT genes and *Lactobacillus*, *Escherichia*, *Blautia*, *Alistipes*, *Bacteroides* and *Bifidobacterium* amongst others (54).

## LIMITATIONS

The current report presents results from an interim analysis of a long term prospective study, and the present sample size is small. The small sample size raises concerns about the reliability and consistency of the present results which will need to be addressed in a larger sample. Because of the small sample size, we were not able to control for the effect of confounders including changes in diet after surgery, which is known to be a major factor determining gut microbiota composition and function. Potential variations across the menstrual cycle were also not taken into account. Furthermore, our results show only the early effects of sleeve gastrectomy on weight, appetite, hedonic eating and gut microbial composition. Longitudinal follow-up is necessary to evaluate whether these findings are sustained over time. Although the instruments used here to measure food addiction including YFAS have been validated in lean and obese populations and are used broadly to study hedonic eating, subjects may feel uncomfortable reporting truthfully their struggle with high-hedonic value foods.

## CONCLUSIONS

Laparoscopic sleeve gastrectomy results in early and dramatic reductions in weight, body fat mass, food intake and hunger levels. In addition, the procedure significantly reduced measures of hedonic eating including food addiction scales, and preference for high-calorie foods. In this preliminary analysis, the postoperative changes in weight, appetite and hedonic eating were associated with alterations of the gut microbial composition suggesting that surgically induced perturbations in gut microbiota-brain interactions axis may play an important role as mediators of the effects of bariatric surgery. Further analysis in a larger cohort with additional time points and assessment of metabolite changes are required to fully characterize the molecular mechanisms underlying sustained weight loss following bariatric surgery.

## Acknowledgments

This study is funded in part by the NIH/NCATS UCLA CTSI -UL1TR000124

## Abbreviations

<b>BMI</b>	Body Mass Index
<b>Log<sub>2</sub>FC</b>	Log <sub>2</sub> fold change
<b>LSG</b>	Laparoscopic Sleeve Gastrectomy
<b>NHANES</b>	National Health and Nutrition Examination Survey
<b>OTUs</b>	Observable Taxonomic Units
<b>SCFAs</b>	Short Chain Fatty Acids
<b>sPLS-DA</b>	Partial Least Square-Discriminant Analysis (sPLS-DA)
<b>UCLA</b>	University of California Los Angeles
<b>VAS</b>	Visual Analogue Scale
<b>VIP</b>	Variable importance in projection
<b>YFAS</b>	Yale Food Addiction Scale

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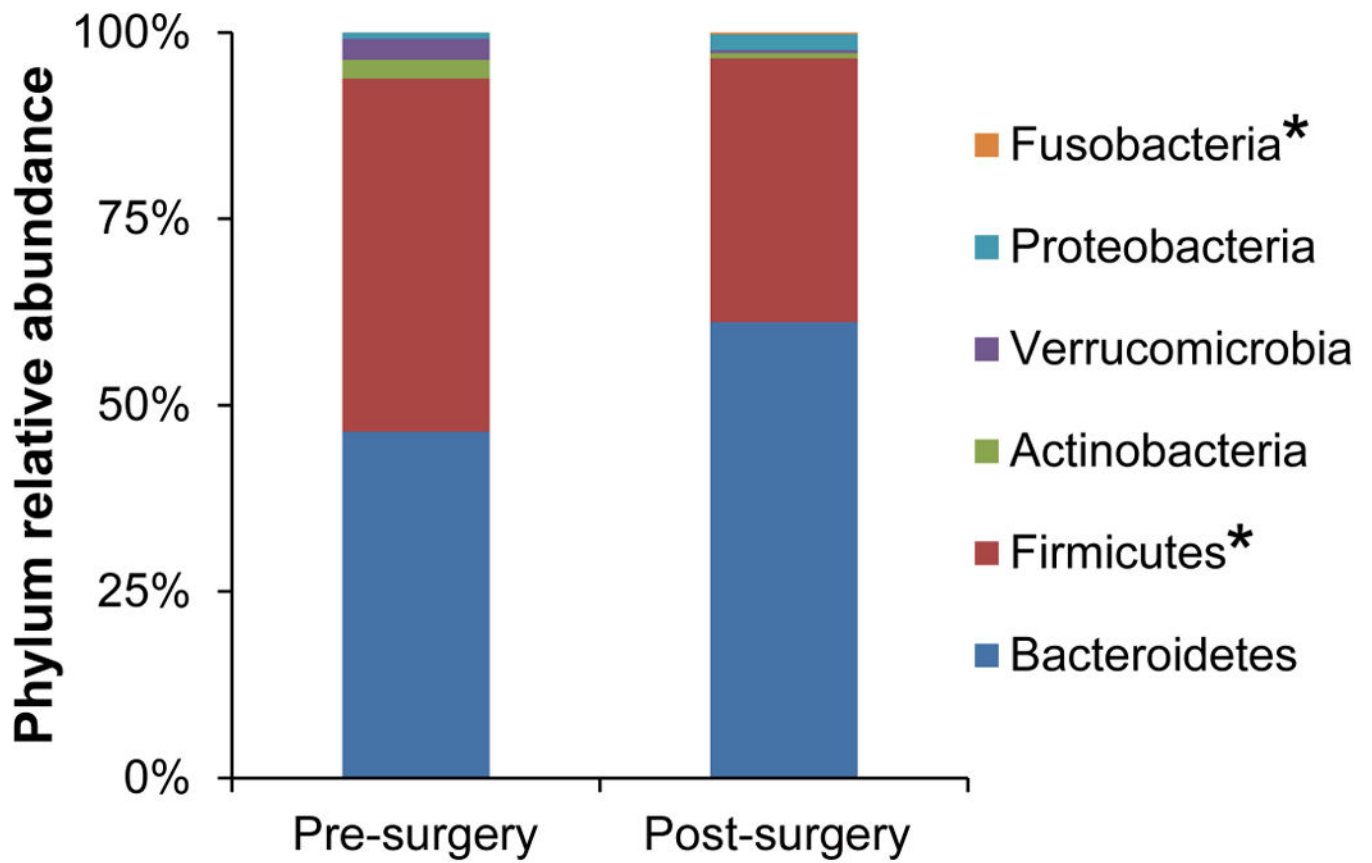
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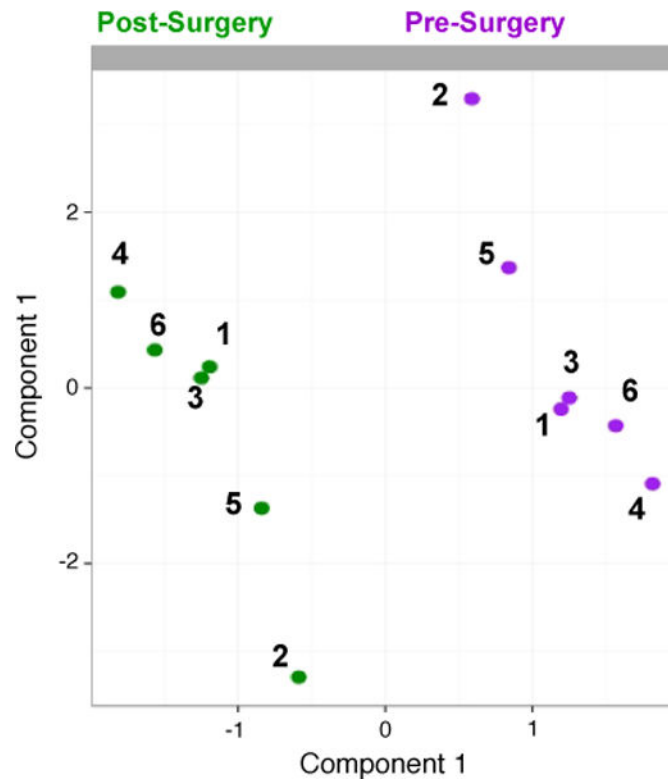


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**Figure 1. Changes in the relative abundance of gut microbiota after Sleeve Gastrectomy**  
LSG results in changes in the relative abundance at the phylum level. The relative abundance of only 2 of the major phyla (Firmicutes and Fusobacteria) changed significantly after surgery. \* $q < 0.05$



**Figure 2. Gut microbial signature discriminates surgical status**

Sample representation from multilevel sPLS-DA. Samples were projected onto a subspace spanned by the first and second sPLS-DA component, based on the 5 genus-level taxa selected on the components. Dots and numbers represent individuals, purple color codes for pre-operative status and green color for post-operative status.

Bacterial Genera	Postoperative Change in Variables				
	BMI	Fat Mass	Hunger (Fasting)	YFAS	Desire for Sweets
Akkermansia			Dark Red		Light Green
Acidaminococcus	Light Green				
Anaerostipes			Dark Green	Dark Red	
Bifidobacteriaceae	Light Green				
Bilophila		Light Green			
Butyrivibrio	Light Green		Dark Red	Light Green	
Catenibacterium				Dark Red	
Collinsella	Light Green				
Dialister	Dark Red	Dark Red			
Enterococcus	Dark Red	Dark Red	Dark Red	Light Green	
Eubacterium	Light Green	Dark Green		Dark Red	
Faecalibacterium	Light Green	Light Green			Dark Red
Haemophilus	Dark Red	Dark Red			
Holdemania	Light Green	Light Green			
Lachnospira	Light Green	Light Green			
Methanobrevibacter	Light Green	Light Green			
Odirobacter			Dark Red	Light Green	
Paraprevotella				Dark Green	Dark Green
Roseburia	Dark Red	Dark Red			
Synergistes	Dark Green	Light Green			

**Figure 3. Associations between gut microbial genera and changes in clinical variables at 1 month after LSG**

This heatmap shows the significant associations between bacterial genera and post-surgical changes in clinical variables after LSG. Correlations were adjusted for multiple hypothesis testing and considered significant at a false discovery rate of 5%. The red color indicates significant positive correlations, the green color indicates significant negative correlations, and the black color indicates non-significant correlations. Darker shades of red or green indicate correlations with false discovery rate between 5 and 10%.

**TABLE 1**

Effect of bariatric surgery on measures of obesity, appetite and hedonic eating.

Variable	Before surgery (mean±SD) N=8	After surgery (mean±SD) N=8	P value
<b>Obesity measures</b>			
BMI (kg/m <sup>2</sup> )	43.4±6.0	38.8±6.3	**<0.001
Body fat mass (kg)	52.9±14.1	44.8±13.5	*0.009
<b>Appetite measures</b>			
Hunger at fast	72.5±10.3	41.25±24.7	*0.003
Food intake (calories/day)	1837.5±514.7	676.5±350.7	*0.006
Fat intake (calories/day)	658.9±257.2	201.8±169.8	*0.012
Carbohydrates intake (calories/day)	830.2±249.4	262.8±183.0	*0.007
<b>Hedonic eating measures</b>			
YFAS score (symptom count)	4.3±2	1.1±0.3	*0.015
Desire to eat high-calorie foods	7.5±1.2	4.5±2.0	*0.018
Desire to eat low-calorie foods	5.1±1.7	5.5±1.6	0.734

Data were collected at baseline and 1-month after surgery. Surgery had a profound effect in measures of obesity, appetite and hedonic eating. YFAS (Yale Food Addiction Scale)

\* Significant, p<0.05

\*\* Significant, p<0.001

**TABLE 2**  
**List of the genera comprising the discriminative microbial signature**

A microbial signature that discriminates between pre- and postsurgical status was found after analyzing stool samples from 6 participants. The discriminative microbial signature is summarized in this table using variable loadings and variable importance in projection (VIP) coefficients. Each variable loading indexes the relative importance of that genus in the signature for group discrimination between pre and post-surgical status and VIP scores represent contribution of each feature relative to the variance explained by all selected signatures. Negative loadings indicate increase in relative abundance of that genus after surgery.

Genus	VIP	Load
Atopobium	10.19953	-0.89802
Bacteroides	4.653624	-0.40973
Bulleidia	1.32918	-0.11703
TG5	1.069011	-0.09412
Epulopiscium	0.635539	-0.05596