Clinical Factors Associated with Weight Loss Outcomes after Roux-en-Y Gastric Bypass Surgery

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Objective: Gastric bypass surgery is an effective therapy for extreme obesity. However, substantial variability in weight loss outcomes exists that remains largely unexplained. Our objective was to determine whether any commonly collected preoperative clinical variables were associated with weight loss following Roux-en-Y gastric bypass (RYGB) surgery.

Methods: The analysis was based on a prospectively recruited observational cohort of 2,365 patients who underwent Roux-en-Y gastric bypass surgery from 2004 to 2009. Weight loss was stratified into three major phases, early (0-6 months), nadir, and long-term (>36 months). Multivariate regression models were constructed using a database of over 350 variables.

Results: A total of 12-14 preoperative variables were independently associated ($P < 0.05$) with each of the temporal weight loss phases. Preoperative variables associated with poorer nadir and long-term weight loss included higher baseline BMI, higher preoperative weight loss, iron deficiency, use of any diabetes medication, nonuse of bupropion medication, no history of smoking, age >50 years, and the presence of fibrosis on liver biopsy.

Conclusions: Several variables previously associated with poorer weight loss after RYGB surgery including age, baseline BMI, and type 2 diabetes were replicated. Several others suggest possible clinical interventions for postoperative management of RYGB patients to improve weight loss outcomes.

Introduction

Roux-en-Y gastric bypass (RYGB) surgery can induce a substantial weight loss that is associated with improvement in type 2 diabetes, decreased incidence of cancer, improved quality of life, and decreased mortality (1-6). Although the safety and potential efficacy of this procedure are well established (7), some patients may regain variable amounts of weight after a relatively short period of rapid weight loss and remain extremely obese, while others fail to lose significant weight despite the major anatomic and physiological effects from the RYGB surgical intervention (8-10). This has created an increasing emphasis on postoperative medical management, for which little empirical data exists. In addition, recent data from the 2009 to 2010 National Health and Nutrition Examination Survey (NHANES) (11), using measured heights and weights, indicate that 15.5% of all US adults greater than 20 years of age have a BMI $\geq 35$ kg/m$^2$ and that 6.3% have a BMI $\geq 40$ kg/m$^2$ and therefore meet existing eligibility criteria for RYGB surgery (12). Thus, there are a substantial number of patients with extreme obesity for whom RYGB may be considered and a corresponding growing clinical need to provide evidence-based guidance on the selection of treatment modalities.

Previous studies have attempted to identify factors associated with weight loss outcomes (13,14). A variety of socioeconomic, psychological, and biological variables have been analyzed (15). The clinical variable with the strongest effect is baseline BMI; the higher the...
BMI, the more likely the patient will lose less of a percentage of excess body weight relative to patients with lower initial BMIs. This effect is in part an artifact of measuring weight loss in relative rather than absolute terms (16,17). However, patients with very extreme levels of obesity, that is, “super-obesity,” may represent a different biological state than those with less severe obesity (18). Other factors, such as diabetes, psychological conditions, and limited physical activity, may also be associated with poorer weight loss outcomes after RYGB surgery. Most studies of preoperative clinical predictors have analyzed only one or a few potential variables often in small populations, ranging up to analysis of 20 variables in 300 patients (13,15). These studies have also had a relatively short length of follow-up, often only up to 1 year, and examined weight loss at a single time point.

We analyzed the association of more than 350 variables with the weight loss dynamics of more than 2,000 patients over a follow-up period of more than 36 months stratified into three major phases, early weight loss, weight nadir, and long-term weight loss, in order to construct multivariate regression models.

Methods

Study population

All patients who entered the bariatric surgery program in the Center for Nutrition and Weight Management at Geisinger Clinic were consecutively offered participation in an IRB approved research program focused upon obesity. All study participants provided written informed consent. Patients who underwent RYGB gastric bypass surgery from January 1, 2004 through August 22, 2011 were included in the analysis. The bariatric surgery program consisted of a preoperative program that typically lasted 6-12 months and included a diet-induced weight loss target of 10% of body weight (Supplementary Methods). Patients were scheduled for follow-up visits at the Geisinger Weight Management Clinic at approximately 1 week, 2 weeks, 2 months, 5 months, 8 months, and 12 months after RYGB surgery, and then every 6-12 months thereafter.

Study variables

Data used for this study were obtained from several clinical sources and entered into an IRB approved database on RYGB patients enrolled in the obesity research program of the Geisinger Obesity Research Institute. The detailed methods for acquiring and storing these data are described elsewhere (19). Briefly, clinical data were extracted from an electronic health record (EHR) fed comprehensive enterprise-level data warehouse, the Clinical Decision Intelligence System (CDIS), which contained a variety of data from the EHR (EpicCare® EHR; Verona, WI). Additional self-administered survey data were obtained during the preoperative period. The database also included results of intraoperative liver biopsy pathology analysis and preoperative clinical ratings by dieticians to determine whether patients were prepared to make necessary dietary changes, and by psychologists to determine if patients were psychologically prepared for the RYGB surgery and lifestyle changes. Details regarding the data used for the study are provided in the Supplementary.

Postoperative weight measures were carefully reviewed to identify and remove implausible or inconsistent values as described previously (19). To evaluate weight loss after RYGB, weight change was quantified as percent of initial excess body weight lost (%EBWL). To calculate excess body weight (EBW), the weight at the visit occurring closest but before surgery (weight<0) was compared to an ideal body weight of BMI = 25 kg/m². The %EBWL at time t after surgery was calculated as:

\[ \%EBWL = \frac{weight_t - weight_0}{EBW} \]

where weight, was the weight measured at time t.

Statistical analysis

Descriptive statistics of the study population were computed using means, standard deviation, and percentages, as appropriate. Quantile regression (20) was used to estimate the overall median %EBWL after RYGB surgery. Weight loss measures were calculated for each patient within each of three postsurgery weight loss phases. A repeated measures regression model (using random effects to calculate slope and intercept for each patient) was used to estimate the %EBWL achieved at 6 months following surgery. The maximum weight loss achieved between 6 and 36 months after surgery was identified by selecting the lowest BMI from at least three available measurements. When this value was not the last measurement within this span, it was defined as the maximal %EBWL nadir. Patients whose last measurement in the 6-36 month period was the lowest were excluded from the analysis of weight nadir (a total of 25%, most of which were less than 36 months post-RYGB and had not yet reached weight nadir). The weight measure occurring after but closest to 36 months was used to evaluate long-term weight loss. For each weight loss phase, analyses were limited to the subset of the population with a qualifying weight loss outcome metric (see Supplementary Methods Regression Analysis).

Baseline regression models included a categorical variable for initial BMI (grouped as 35-39.9, 40-49.9, 50-59.9, and 60+ kg/m²). This variable was selected because baseline BMI is well known to be associated with degree of weight loss following RYGB surgery (15) and may be correlated with some of the clinical variables. Each of the over 350 clinical variables (Supplementary Data) was included in a separate regression model to identify the subset that was significantly related to each temporal weight loss phase after accounting for baseline BMI using a P-value < 0.05 (Supplementary Data).

Results

Demographics

The demographics of the initial study cohort, consisting of 2444 patients who had undergone RYGB surgery and had an initial BMI > 35 kg/m², are shown in Supplementary Table S1. The mean age was 46 years (range 18-74), 81% were female, 97% were Caucasian, and the mean baseline BMI was 49.6 kg/m² (range 35-94.3). Patients with 4 or more weight measures after surgery were included in the analyses, with an average of 21 weight measures/patient and a range of 4-203.

Weight loss analysis

Many prior studies have analyzed only one or few distinct postoperative time points, for example, 12 and/or 24 months. We (18,21) and others (22) have used more advanced statistical methods to
evaluate weight loss after surgery, including analysis of postoperative weight loss trajectories using linear mixed models (21,22) to model weight loss dynamics over time. We identified three distinct phases of postoperative weight loss; an initial steep weight loss followed by an extended period of more gradual weight loss in which a nadir or low point occurs transitioning to a period characterized by some degree of weight regain occurring at about 24-36 months and later (Figure 1). We divided the available weight loss data into these three weight loss phases and conducted an analysis of %EBWL as follows:

- Early: The first 6 months after surgery where rapid weight loss occurs
- Nadir: The maximal %EBWL achieved that occurs between 6 and 36 months after surgery
- Long-term: weight loss at 36 or more months after surgery

Of the 2444 patients, 2365 (97%) had four or more weight measures occurring in the first 6 months after surgery, 1369 (56%) had sufficient weight measurements to identify a weight loss nadir (at least three weight measures between 6 and 36 months after surgery, the last of which was not the lowest), and 857 of 1361 patients who were more than 36 months from surgery (60%) and had at least one weight measure occurring 36 or more months after surgery. To determine whether the differences in data density affected the population substructures, we evaluated the demographic characteristics and later (Figure 1). We divided the available weight loss data into these three weight loss phases and conducted an analysis of %EBWL as follows:

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Six month weight loss
Multiple linear regression analysis using the 98 variables brought forward from initial univariate analysis revealed 14 preoperative variables (P-value < 0.05) that were independently associated with lower early weight loss (Table 1). The magnitude of the effect (as measured using the parameter estimates from the multivariate linear regression) was largest for baseline BMI, in which those with BMI < 40 kg/m² had 43.3% more %EBWL, preoperative weight gain, in which those who gained weight during the preoperative period had 8.9% less %EBWL, and liver fibrosis, in which those with a baseline BMI of less than 50 kg/m² had 8.8% less %EBWL.

Weight nadir
Of the 69 univariate variables, a total of 12 clinical variables were independently associated (P < 0.05) with higher weight nadir (Table 2). The magnitude of the effect was largest for the same variables as for 6 months weight loss but to different degrees; for baseline BMI, those with BMI < 40 kg/m² had 40.8% more %EBWL, those who gained weight during the preoperative period had 10.7% less %EBWL, and those with liver fibrosis and a baseline BMI of less than 50 kg/m² had 10.6% less %EBWL.

36+ Month weight loss
A total of 12 of 44 univariate clinical variables were independently associated with (P < 0.05) less long-term %EBWL at least 36 months after RYGB surgery (Table 3). The magnitude of the effect was largest for baseline BMI (40.9% more %EBWL for those with BMI < 40 kg/m²), any fibrosis on liver biopsy (those with a baseline BMI of less than 50 kg/m², 13.4% less %EBWL), age 50 years or older with open surgical access (9.5% less %EBWL), and nonusers of bupropion medication (6.4% less %EBWL).

We then used the multivariate regression results to develop equations to estimate %EBWL for each temporal weight loss phase (Supplementary data). The equation to determine the predicted amount of long-term %EBWL is:

Long-term%EBWL = 56.7 + 40.9*BMI35 + 16.4*BMI40 + 3.5*BMI50–5.3*DiabetesMed + 6.4*bupropion + 4.8*smoker–9.5*age50*open – 3.9*age49*lap–4.9*age49*open – 13.4*fibrosis*BMI35–13.4*fibrosis*BMI40–0.1*fibrosis*BMI50–0.1*fibrosis*BMI60.

where, BMI35 = 1 if baseline BMI 35-39.9, else = 0
TABLE 1 Clinical variables associated with 6 month weight loss (N = 2365)

| Variable                                    | Estimate | SE  | P-value |
|---------------------------------------------|----------|-----|---------|
| Intercept                                   | 58.3     | 3.3 |         |
| Baseline BMI                                |          |     |         |
| 35-39.9                                     | 43.3     | 1.6 | <0.0001 |
| 40-49.9                                     | 23.1     | 1.2 | <0.0001 |
| 50-59.9                                     | 8.9      | 1.1 | <0.0001 |
| >60+                                        | Reference|     |         |
| Preoperative weight loss                    |          |     |         |
| >0% gain                                    | -8.9     | 1.0 | <0.0001 |
| 0-5% loss                                   | -6.3     | 1.0 | <0.0001 |
| 5-10% loss                                  | -6.5     | 1.0 | <0.0001 |
| 10-19% loss                                 | -5.0     | 0.9 | <0.0001 |
| 20%+ loss                                   | Reference|     |         |
| Surgical access                             |          |     |         |
| Open surgery                                | -5.3     | 0.7 | <0.0001 |
| Laparoscopic surgery                        | Reference|     |         |
| Age                                         |          |     |         |
| 18-39 Referential                           | Reference|     |         |
| 40-49 Referential                           | -2.0     | 0.8 | 0.0117  |
| 50-59 Referential                           | -4.4     | 0.8 | <0.0001 |
| >60+ Referential                            | -7.4     | 1.1 | <0.0001 |
| Waist circumference                         |          |     |         |
| <45 Referential                             | 6.0      | 1.7 | 0.0004  |
| 45-49 Referential                           | 2.8      | 1.2 | 0.0238  |
| 50-54 Referential                           | 0.7      | 1.2 | 0.524   |
| 55-59 Referential                           | -0.3     | 1.2 | 0.797   |
| >60+ Referential                            | Reference|     |         |
| Time from baseline visit to surgery         | -3.8     | 1.4 | 0.0091  |
| Cholesterol HDL ratio                       |          |     |         |
| <4 Referential                              | -1.8     | 0.8 | 0.0255  |
| 4-4.9 Referential                           | 0.1      | 0.9 | 0.873   |
| 5+ Referential                              | Reference|     |         |
| Smoking history                             |          |     |         |
| Yes Referential                             | 2.3      | 0.7 | 0.0015  |
| Co-morbidity burden                         |          |     |         |
| Each additional ICD9 code                  | -0.3     | 0.1 | 0.0472  |
| Diabetes group                              |          |     |         |
| Any Insulin Sens Agent medication           | -1.9     | 1.0 | 0.0462  |
| Public distress                             |          |     |         |
| Low distress score                          | -1.5     | 0.7 | 0.0352  |
| Anisocytosis (red blood cells of unequal size) | -3.0 | 0.9 | 0.0011  |
| Red cell distribution width >15%            |          |     |         |
| Certainty of commitment to weight loss program | 2.5  | 1.0 | 0.0145  |
| Extremely certain (WLRQ2=5)                 |          |     |         |
| Liver pathology and baseline BMI            |          |     |         |
| No fibrosis                                 | Reference|     |         |
| Any Fibrosis with baseline BMI<50 kg/m2     | 8.8      | 1.9 | <0.0001 |
| Any Fibrosis with baseline BMI 50+ kg/m2    | 2.2      | 2.0 | 0.271   |

For example, a 47-year-old (age 50, smoking status=0) non-smoker (smoker=0) with a BMI of 56 (BMI50 = 1) who used diabetes medications (DiabetesMed = 1) preoperatively but not bupropion (bupropion=0) who underwent laparoscopic RYGB (lap = 1; open = 0) and did not have fibrosis on liver biopsy (fibrosis = 0) would have the following predicted %EBWL:

Long-term %EBWL = 56.7 + 40.9*0 + 16.4*0 + 3.5*1 + 5.3*1 + 6.4*0 + 4.8*0 + 9.5*0 - 3.9*1*1 - 4.9*1*0 - 13.4*0 - 13.4* 0*0 - 0.1*1*1 + 0.1*0*0.0.

Long-term %EBWL = 56.7 + 0 + 0 + 3.5 - 5.3 + 0 + 0 - 3.9 - 0 - 0 - 0 - 0. 0.

Long-term %EBWL = 56.7 + 3.5 - 5.3 - 3.9

Long-term %EBWL = 51.0

We also determined whether the model suggested an appropriate fit using a residual plot (Supplementary Figure S2). The plot indicates that the model is homoscedastic, that is, that the variation in residuals was independent of the predicted value, and that the model is unbiased, that is, the values of the residuals were independent of the predicted values.

**Discussion**

The degree of weight loss that is achieved by patients who undergo RYGB surgery, even in the context of a highly standardized clinical program with excellent long-term follow up, may vary, suggesting that patient-specific factors may play a role in influencing weight loss outcomes. Previous studies have examined a wide variety of socioeconomic (20), psychological (12), procedural (16), and genetic factors (18,21) in an effort to identify variables which may influence the degree of postoperative weight loss. A recent systematic analysis focused on preoperative BMI, preoperative weight loss, eating disorders, and psychological factors/substance abuse (15). However, most of the available data has been based on small sample sizes with relatively short-term follow-up and analysis of single postoperative time points (e.g., 12 months). We studied a large cohort followed for over 3 years with a large database of clinical variables.

We found that baseline BMI was inversely associated with %EBWL at the early phase of weight loss as well as with weight nadir, the lower the BMI the more the %EBWL. This is consistent with data
TABLE 2 Clinical variables associated with weight loss nadir (N = 1369)

|                          | Estimate | SE  | P-value   |
|--------------------------|----------|-----|-----------|
| Intercept                | 75.1     | 3.3 |           |
| Baseline BMI             |          |     |           |
| 35-39.9                  | 40.8     | 3.2 | <0.0001   |
| 40-49.9                  | 22.4     | 2.3 | <0.0001   |
| 50-59.9                  | 8.7      | 2.2 | <0.0001   |
| 60+                      |          |     |           |
| Preoperative weight loss |          |     |           |
| >0% gain                 | -10.3    | 1.9 | <0.0001   |
| 0-5% loss                | -6.5     | 1.9 | 0.0007    |
| 5-10% loss               | -7.0     | 1.9 | 0.0002    |
| 10-19% loss              | -6.1     | 1.6 | 0.0002    |
| 20%+ loss                |          |     |           |
| Diabetes group           |          |     |           |
| No diabetes              | Reference|     |           |
| Diabetes with HbA1c<9    | -4.4     | 1.3 | 0.0009    |
| Diabetes with HbA1c>=9   | -8.4     | 2.6 | 0.0012    |
| Age                      |          |     |           |
| 18-39                    | Reference|     |           |
| 40-49                    | -3.7     | 1.5 | 0.0142    |
| 50-59                    | -5.0     | 1.6 | 0.0018    |
| 60+                      | -8.6     | 2.1 | <0.0001   |
| Surgical access          |          |     |           |
| Open surgery             | -3.2     | 1.2 | 0.0082    |
| Laparoscopic surgery     | Reference|     |           |
| Waist circumference      |          |     |           |
| <45                      | 6.5      | 3.0 | 0.0309    |
| 45-49                    | 0.4      | 2.3 | 0.860     |
| 50-54                    | -1.7     | 2.1 | 0.429     |
| 55-59                    | -1.7     | 2.1 | 0.416     |
| 60+                      | Reference|     |           |
| Use of bupropion         |          |     |           |
| Active use of medication | 6.2      | 2.0 | 0.0015    |
| Iron deficiency          |          |     |           |
| Low Transferrin saturation| -4.6     | 2.1 | 0.0296    |
| (<15% men, <12% women)   |          |     |           |
| Cholesterol HDL ratio    | <4       |     | 0.0107    |
|                          | 4-4.9    | 1.6 | 0.0092    |
|                          | 5+       |     |           |
| Motivated to lose weight (WLRQ1) |       |     |           |
| Extremely motivated compared to previous attempts | 5.1 | 2.0 | 0.0109 |
| Hypertension             |          |     |           |
| Active diagnosis         | -2.8     | 1.2 | 0.0200    |
| Liver pathology and baseline BMI |          |     |           |
| No fibrosis              | Reference|     |           |
| Any Fibrosis with baseline BMI <50 kg/m² | -10.6 | 3.3 | 0.0015 |
| Any Fibrosis with baseline BMI 50+ kg/m² | -1.6 | 3.6 | 0.651 |

We used percentage of excess body weight (%EBWL) as the measure of weight loss, recommended as the standard metric (17). However, %EBWL is a relative measure that diminishes the significance of the absolute amount, that is, pounds, of weight lost. BMI is directly correlated with health risks (23), thus the lower the BMI the less the risk. The disparity between %EBWL and other weight loss measures such as absolute weight loss is also likely magnified by the length of postoperative follow-up. The relatively short lengths of follow-up (i.e., 12 months) of many studies may not allow sufficient time for patients with higher BMIs to shed sufficient number of pounds to reach their weight nadir.
The majority of prior published studies have used only one or few distinct postoperative time points, for example, 12 and/or 24 months. We (18,21) and others (22) have used more advanced statistical methods to evaluate weight loss after surgery. Here we chose a hybrid approach and used longitudinal weight loss data to identify three distinct temporal phases of weight loss following RYGB surgery, including early weight loss (i.e., the first 6 months after surgery), weight loss nadir, and long-term weight loss (i.e., >36 months after surgery). This also allowed us to evaluate the relationship of short-term weight loss to long-term. We found that the unadjusted correlation ($r^2$) between %EBWL at 6-months and 36+ months was 0.545. This also extends to preoperative weight loss where we found a similar effect, with preoperative weight loss significantly associated with 6-month and weight nadir outcomes (Tables 2 and 3), but not with weight loss at >36 months. This is consistent with the results of systematic analyses (15) which found that patients who lost more weight preoperatively also lost more excess weight at 12 months following surgery, but not at longer follow-up periods. These data support the notion that long-term weight loss outcomes may be largely independent of short-term weight loss success.

We confirmed the association of type 2 diabetes with lower %EBWL that has been previously reported (13,14,24). We also found that the potentially related finding of liver fibrosis was related to lower %EBWL but only in patients with BMI < 50 kg/m². Liver fibrosis is part of the spectrum of non-alcoholic steatohepatitis, which has been related to insulin resistance (25). Our data are consistent with the finding that liver fibrosis measured noninvasively via the Fibrospect score II, which is comprised of plasma levels of alpha 2 macroglobulin, hyaluronic acid and tissue inhibitor of metalloprotease 2, was the only predictor of weight loss in study of a Hispanic RYGB population (26). Whether hepatic fibrosis is independent of the influence diabetes is not yet known.

We also found that waist circumference, cholesterol HDL ratio, and red cell distribution width (RDW) and iron deficiency were associated with both early weight loss and weight nadir. Waist circumference was highly correlated with BMI, but its lack of association at ≥36 months suggests a potential physiological effect from the presumed higher burden of metabolically active visceral fat. Dyslipidemia has been associated with lower weight loss following bariatric surgery (14). The association of iron deficiency (and its red blood cell correlate RDW) with less %EBWL suggests that this treatable condition should be carefully evaluated in patients undergoing RYGB, and perhaps more generally in patients undergoing weight loss interventions, especially premenopausal female patients in situations of decreased food and nutrient intake. Hypertension and less motivation to lose weight were specific to weight nadir. The individuals who have the highest level of motivation to lose weight appear to reach the lowest weight nadir. The role of hypertension is not clear.

Two other clinical observations related to long-term weight loss were a history of smoking and the preoperative use of bupropion. Smoking history has been associated with an increased risk of serious complications (life threatening and/or associated with lasting disability) within 30 days of bariatric surgery (27). In patients presenting for bariatric surgery, previous attempts to quit smoking were associated with substantial weight gain (28). Bupropion was originally developed to treat depression (29) but was found to be effective for smoking cessation (30) and has recently been used for the treatment of obesity (31,32). The association of these two clinical factors with increased weight loss following RYGB suggests that common pathways may be involved in their mechanism. Bupropion is a dopamine and norepinephrine reuptake antagonist and a putative stimulator of melanocortin pathways (33). Nicotine has been found to decrease food intake and body weight in mice via the hypothalamic melanocortin system (34). Melanocortin-4 receptor variants have been associated with weight loss outcomes after RYGB (35), further implicating this pathway underlying the molecular mechanism of variability in weight loss response.

Strengths of this study include the standardization of the RYGB surgical technique and the pre- and postoperative management program, large numbers of patients, and high rate and length of postoperative follow-up. However, several limitations are evident. The design was not randomized and the sex distribution was skewed toward women, characteristic of a bariatric surgery cohort. We only analyzed RYGB and not other weight loss interventions, and %EBWL was the only a postoperative outcome. RYGB has multiple and pleiotropic effects on a number of conditions, particularly type 2 diabetes, dyslipidemia, hypertension, and others. Despite the breadth and depth of the clinical data used in our analyses, we did not have variables outside of clinical standard of care. This includes information on physical activity. Physical activity is a major factor in energy expenditure and may play a significant role in post-RYGB weight loss (30). We did not have data available from either self-reported measures of physical activity, or from objective monitors such as pedometers, accelerometers, or other devices. Given the potential importance of physical activity in weight loss outcomes, future studies will need to be performed to gather such data. Despite these limitations, these data suggest that preoperative data may be used for the early recognition of clinical factors that adversely impact post-RYGB weight loss. The limited access to surgical treatment for eligible extremely obese patients, the ever-expanding list of procedure options, and the wide range of weight loss outcomes mandates improved patient selection as well as better resource allocation for peri-operative medical management. The identification of the clinical factors, which adversely impact post-RYGB weight loss will allow for the implementation of specific therapeutic strategies and clinical trials designed to address the underlying basis of unfavorable outcomes.

Conclusion
In summary, the early, nadir, and long-term weight loss phases following RYGB surgery were associated with different sets of easily measured preoperative clinical variables. The variables associated with less %EBWL at least 36 months after RYGB surgery were higher baseline BMI, preoperative use of any diabetes medication, non-use of bupropion medication, no history of smoking, age greater than 50 years, and the presence of fibrosis on liver biopsy. These data suggest that specific therapeutic strategies may be designed to address the factors associated with unfavorable outcomes.

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References

1. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;292:1724-1737.

2. Sjostrom CD. Systematic review of bariatric surgery. *JAMA* 2005;293:1726.

3. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2004;351:2683-2693.

4. Clegg A, Colquitt J, Sidhu M, Royle P, Walker A. Clinical and cost effectiveness of surgery for morbid obesity: a systematic review and economic evaluation. *Int J Obes Relat Metab Disord* 2003;27:1167-1177.

5. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683-2693.

6. Ali MR, Fuller WD, Chiu MP, Wolfe BM. Bariatric surgical outcomes. *Surg Clin North Am* 2005;85:839-852.

7. Dixon JB, Straznicky NE, Lambert EA, Schlaich MP, Lambert GW. Surgical approaches to the treatment of obesity. *Nat Rev Gastroenterol Hepatol* 2011;8:429-437.

8. Porjes WJ, Swanson MS, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 1995;222:339-350; discussion 50-2.

9. Christou NV, Look D, Maclean LD. Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. *Ann Surg* 2006;244:734-740.

10. Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: surgical treatment of obesity. *Ann Intern Med* 2005;142:547-559.

11. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2000. *JAMA* 2012;307:491-497.

12. Elmore BL, Phillips WT. Bariatric Surgery coverage decision: opportunities and limitations. *Healthc Financ manage* 2006;60:52-54.

13. Hatoun NJ, Stein HK, Merrifield BF, Kaplan LM. Capacity for physical activity predicts weight loss after Roux-en-Y gastric bypass. *Obesity* 2009;17:92-99.

14. Junior WS, do Amaral JL, Nonino-Borges CB. Factors related to weight loss up to 4 years after bariatric surgery. *Obes Surg* 2011;21:1724-1730.

15. Livhits M, Mercado C, Yermilov I, et al. Preoperative predictors of weight loss following bariatric surgery: systematic review. *Obes Surg* 2012;22:70-89.

16. van de Laar A, de Caluwe L, Dillemans B. Relative outcome measures for bariatric surgery. Evidence against excess weight loss and excess body mass index loss from a series of laparoscopic Roux-en-Y gastric bypass patients. *Obes Surg* 2011;21:763-767.

17. Bray GA, Bouchard C, Church TS, et al. Is it time to change the way we report and discuss weight loss? *Obesity* 2009;17:619-621.

18. Still CD, Wood GC, Chu X, et al. High allelic burden of four obesity SNPs is associated with poorer weight loss outcomes following gastric bypass surgery. *Obesity* 2011;19:1676-1683.

19. Wood G, Chu X, Manney C, et al. An electronic health record-enabled obesity database. *BMJ Med Inform Decis Mak* 2012;42:45.

20. Koenker R, Bassett GW. Regression quantiles. *Econometrica* 1978;46:33-50.

21. Matzko ME, Argyropoulos G, Wood GC, et al. Association of ghrelin receptor promotor polymorphisms with weight loss following Roux-en-Y gastric bypass surgery. *Obes Surg* 2012;22:783-790.

22. Dallal RM, Quebbemann BB, Hunt LH, Braitsman LE. Analysis of weight loss after bariatric surgery using mixed-effects linear modeling. *Obes Surg* 2009;19:732-737.

23. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373:1083-1096.

24. Melton GB, Steele KE, Schweitzer MA, Lidor AO, Magnuson TH. Suboptimal weight loss after gastric bypass surgery: correlation of demographics, comorbidities, and insurance status with outcomes. *J Gastrointest Surg* 2008;12:250-255.

25. Cassie S, Menezes C, Birch DW, Shi X, Karmali S. Effect of preoperative weight loss in bariatric surgical patients: a systematic review. *Surg Obes Relat Dis* 2011;7:760-767; discussion 7.

26. Guajardo-Salinas GE, Hilmy A, Martinez-Ugarte ML. Predictors of weight loss and effectiveness of Roux-en-Y gastric bypass in the morbidly obese Hispanic-American population. *Obes Surg* 2008;18:1369-1375.

27. Finks JF, Kole KL, Yenumula PR, et al. Predicting risk for serious complications with bariatric surgery: results from the Michigan Bariatric Surgery Collaborative. *Ann Surg* 2011;254:633-640.

28. Forsbush S, Nof L, Echternach J, Hill C, Rainey J. Influence of activity levels and energy intake on percent excess weight loss after Roux-en-Y gastric bypass. *Obes Surg* 2011;21:1731-1738.

29. Dhillon S, Yang LP, Carran MP. Bupropion: a review of its use in the management of major depressive disorder. *Drugs* 2008;68:653-669.

30. King WC, Bond DS. The importance of preoperative and postoperative physical activity counseling in bariatric surgery. *Exerc Sport Sci Rev* 2013;41:26-35.

31. Billes SK, Greenway FL. Combination therapy with naltrexone and bupropion for obesity. *Expert Opin Pharmacother* 2011;12:1813-1826.

32. Plokowski RA, Nguyen Q, Sundaram U, Nguyen L, Chau DL, St Joer S. Bupropion and naltrexone: a review of their use individually and in combination for the treatment of obesity. *Expert Opin Pharmacother* 2009;10:1069-1081.

33. Greenway FL, Whitehouse MJ, Guttaudaria M, et al. Rational design of a combination medication for the treatment of obesity. *Obesity* 2009;17:30-39.

34. Mineur YS, Abizaid A, Rao Y, et al. Nicotine decreases food intake through activation of POMC neurons. *Science* 2011;332:1330-1332.

35. Mirshahi UL, Still CD, Masker KK, Gerhard GS, Carey DJ, Mirshahi T. The MC4R(I251L) allele is associated with better metabolic status and more weight loss after gastric bypass surgery. *J Clin Endocrinol Metab* 2011;96:E2088-E2096.