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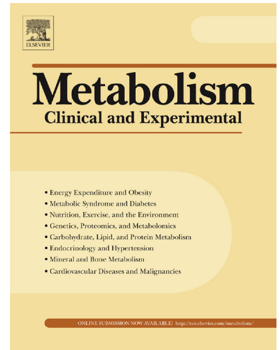

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Personalizing Bariatric Metabolic Surgery: Predictors of Weight-Loss Success and Risk of Weight Recurrence

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ABSTRACT

Background

Bariatric metabolic surgery (Roux-en-Y gastric bypass [RYGB] and sleeve gastrectomy [SG]) effectively treats obesity and type 2 diabetes; however, weight loss varies, necessitating predictive factors.

Methods

We analysed 12- and 24-month weight loss data from 811 patients (RYGB or SG). Factor Analysis of Mixed Data and neural network (NN) modelling identified distinct patient phenotypes and predicted weight-loss patterns. A comparative analysis evaluated weight loss and recurrence between the two procedures.

Findings

RYGB showed significantly greater weight loss than SG at both 12 (30.3% vs. 25.4%; p<0.001) and 24 months (26.3% vs. 21.4%; p<0.001). SG revealed greater variability with bimodal weight loss distributions. Unsupervised clustering of SG patients highligheted three phenotypes: the highest responders were women with favorable metabolic profiles; the lowest responders were mostly men with insulin resistance and diabetes. A NN achieved an overall accuracy of 72.5% in predicting 12-month weight loss from baseline characteristics. In RYGB, clustering was less distinct, though baseline metabolic health influenced weight trajectories. A NN predicted weight recurrence versus sustained loss with 74% accuracy. Poor outcomes were associated with higher baseline glucose, insulin resistance, and dyslipidemia; younger age and absence of diabetes predicted better responses. RYGB was superior to SG, even for metabolic high-risk individuals.

Interpretation

Baseline metabolic health predicts weight-loss outcomes and recurrence risk. RYGB offered greater and more consistent mid-term weight loss, especially benefiting metabolically high-risk patients. Procedure choice must be individualized accounting for specific risk profile and potential complications. These results advocate for a precision-medicine approach in bariatric procedure selection.

Keywords

Bariatric Metabolic Surgery; Weight Loss; Neural Network; Longitudinal Clustering; Mathematical Modelling

1. INTRODUCTION

The World Obesity Atlas projects that global obesity prevalence will reach one billion people by 2030 (https://www.worldobesityday.org/advocacy)[1]. In the United States, class 3 obesity (BMI ≥35 kg/m²) is expected to affect approximately 25% of the population by the same year.[2]

Bariatric metabolic surgery is a cost-effective treatment for obesity, particularly when accompanied by complications such as type 2 diabetes.[3,4,5,6,7]

However, outcomes following bariatric metabolic surgery can vary greatly between individuals. Courcoulas et al.[8] reported a median weight loss of 31.5% after Roux-en-Y Gastric Bypass (RYGB), with results ranging from a 59.2% loss to a 0.9% gain. Similarly, a study comparing RYGB and Sleeve Gastrectomy (SG) highlighted substantial variability in weight-loss outcomes: patients achieved an average weight loss of 32.9% (range: 4.1–60.9%) after RYGB while it averaged 26.2% (range: 1.1–58.3%) after SG.[9]

This variability underscores the desirability to personalize health management. Predictive models can play a crucial role in optimizing resource allocation and guiding decision-making for both clinicians and patients, ultimately improving treatment outcomes.

A machine learning model capable of predicting individual weight trajectories over a five-year after bariatric metabolic surgery, utilized key preoperative variables, including age, weight, height, smoking habit, the presence and duration of type 2 diabetes, and the type of surgical procedure performed.[10] While this approach demonstrated the feasibility of personalized prediction, it did not fully address the heterogeneity of surgical responses or the mechanisms underlying weight recurrence.

To overcome these limitations, we developed a novel, multi-step analytical framework that combines factor analysis of mixed data (FAMD), clustering, and predictive modeling. By integrating a broad set of baseline clinical variables, this method identifies reproducible phenotypes that reflect the diversity of patients undergoing bariatric surgery. These phenotypes provide a robust basis for quantifying variability in weight trajectories and for predicting both 12 month weight loss and 24 month weight regain, with transparent performance metrics ensuring methodological rigor.

Importantly, our phenotype-by-procedure interaction analyses reveal differential effectiveness of Roux-en-Y gastric bypass and sleeve gastrectomy across subgroups. This design highlights metabolically adverse phenotypes that derive greater benefit from Roux-en-Y gastric bypass, while also identifying a low-risk group capable of achieving durable outcomes with either procedure. Taken together, this work establishes a rigorous and generalizable framework that advances prediction of weight outcomes and strengthens the evidence base for personalized surgical decision-making.

2. MATERIALS AND METHODS

To explore weight-loss and recurrence patterns in a large cohort of patients undergoing either Sleeve Gastrectomy (SG) or Roux-en-Y Gastric Bypass (RYGB), we analyzed data from seven previous cohorts. Each study followed its own predefined schedule of assessments, ranging from limited time points (such as baseline and 12 months) to more frequent evaluations at 3 or 6 month intervals, with one study extending follow-up to 10 years. This heterogeneity in design led to substantial variability in data availability at specific time points, thereby influencing the number of participants eligible for inclusion at each stage of the pooled analysis. Consequently, the analytic sample size varied across time points, with specific inclusion criteria applied to define the population analyzed in each case.

Prior to pooling, all continuous variables from the different studies were harmonized to ensure consistent units of measurement across the entire dataset. This involved, where necessary, systematic conversion to predefined standard units: fasting glucose was converted from mg/dl to mmol/l by dividing by 18; total cholesterol, HDL-cholesterol, and LDL-cholesterol were converted from mg/dl to mmol/l by dividing by 38.67; triglycerides were converted from mg/dl to mmol/l by dividing by 88.57. Furthermore, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was computed from the product of basal glucose (mmol/l) and Insulin (mU/ml) divided by the factor 22.5. All insulin measurements were consistently provided in mU/ml.

2.1 Study cohorts

The number of individuals with weight values at baseline and at 12 month follow-up were 811 (477 RYGB and 334 SG); patients with measurements at baseline and at 24 month follow-up were 400 (274 RYGB and 126 SG); individuals with both 12 and 24 month follow-up weight values beyond the baseline were 367 (257 RYGB and 110 SG).

2.1.1 BRAVES Cohort

BRAVES is a 52-week, open-label, multicenter, randomized controlled trial (RCT) (ClinicalTrials.gov identifier: NCT03524365) designed to assess the efficacy of Roux-en-Y gastric bypass and sleeve gastrectomy for the treatment of Metabolic Dysfunction-Associated Steatohepatitis (MASH) in individuals with obesity, with or without type 2 diabetes. This trial enrolled 288 participants with obesity (BMI 30–55 kg/m²), with or without type 2 diabetes (T2DM), who had histologically confirmed MASH (NAFLD activity score of at least 1 in each component) and no evidence of other forms of liver disease. Demographic data, anthropometric measurements, medical histories, concomitant medications, and laboratory results were collected as previously described.[11] The study protocol received approval from the ethics committees of Fondazione Policlinico A. Gemelli, Policlinico Umberto I, and Azienda Ospedaliera San Camillo-Forlanini in Rome, Italy. Written informed consent was obtained at the time of enrollment and again prior to any surgical procedures.

2.1.2 DIBASY Cohort

DIBASY is a three-group, open-label, RCT (ClinicalTrials.gov identifier: NCT00888836) comparing conventional diabetes management with bariatric metabolic surgery (Roux-en-Y gastric bypass or Bilio-pancreatic diversion) for diabetes remission. This trial enrolled 60 participants with obesity (BMI≥35 kg/m^2), a history of T2DM lasting at least 5 years, glycated hemoglobin A1c (HbA1c) ≥7·0% (≥53 mmol/mol). Demographic characteristics, anthropometric measurements, medical history, concomitant medication and laboratory tests were collected as previously described.[12]

2.1.3 ARGOS Cohort

ARGOS is prospective open-label, RCT (ClinicalTrials.gov identifier: NCT04583683) comparing weight loss achieved through very low-calorie diet or bariatric metabolic surgery

(Roux-en-Y gastric bypass or sleeve gastrectomy). This trial enrolled 218 patients with obesity (≥35 kg/m^2) and at least one or more obesity-related complication such as T2DM, hypertension, sleep apnea and other respiratory disorders, non-alcoholic fatty liver disease, osteoarthritis, lipid abnormalities, gastrointestinal disorders, or heart disease. Demographic characteristics, anthropometric measurements, medical history, concomitant medication and laboratory tests were collected at baseline and after surgical intervention.

2.1.4 OSAPS Cohort

OSAPS is prospective open-label, RCT (ClinicalTrials.gov identifier: NCT03223467) designed to assess the effects of bariatric metabolic surgery (Roux-en-Y gastric bypass or sleeve gastrectomy) on obstructive sleep apnea. This trial enrolled 86 patients aged between 20 and 70 years with obesity (≥30 kg/m^2). Demographic characteristics, anthropometric measurements, medical history, concomitant medication and laboratory tests were collected as previously described.[13]

2.1.5 LETHE Cohort

LETHE is prospective open-label, RCT (ClinicalTrials.gov identifier: NCT03534310) designed to assess the effect of intensive-lifestyle-modification with or without Liraglutide (3mg/day) or sleeve-gastrectomy on weight loss.

This trial enrolled 75 patients aged between 18 and 70 years with obesity (≥35 kg/m^2) and at least one or more obesity-related complication such as T2DM, hypertension, sleep apnea and other respiratory disorders, non-alcoholic fatty liver disease, osteoarthritis, lipid abnormalities, gastrointestinal disorders, or heart disease. Demographic characteristics, anthropometric measurements, medical history, concomitant medication and laboratory tests were collected as previously described.[14]

2.1.6 BARHY Cohort

BARHY is prospective open-label, RCT (ClinicalTrials.gov identifier: NCT01581801) designed to compare the incidence of hypoglycemia after Roux-en-Y gastric bypass or sleeve gastrectomy. In this trial were enrolled 120 patients aged between 25 and 65 years with obesity (≥35 kg/m^2) and at least one or more obesity-related complication such as sleep apnea, severe coxarthritis or gonarthritis, severe hypertension. Demographic characteristics, anthropometric measurements, medical history, concomitant medication and laboratory tests were collected as previously described.[15]

2.1.7 BASTA Cohort

BASTA is prospective open-label, RCT (ClinicalTrials.gov identifier: NCT02331420) aimed at evaluating the effects of weight loss induced by bariatric metabolic surgery (Roux-en-Y gastric bypass) on cardiovascular health. This trial enrolled 58 patients with obesity (≥35 kg/m^2) and at least one or more obesity-related complication such as sleep apnea, severe coxarthritis or gonarthritis, severe hypertension. Demographic characteristics, anthropometric measurements, medical history, concomitant medication and laboratory tests were collected at baseline and following surgery.

All protocols were approved by the ethics committees of Fondazione Policlinico A Gemelli, Rome, Italy. Written informed consent was obtained at enrolment and again before surgical procedures.

2.2 <u>Outcomes</u>

The outcomes of the study were weight loss at 12 and 24 month follow-up as well as percent change in weight and percent weight recurrence calculated as:

$$\%\Delta weight = \frac{weight\ at\ baseline - weight\ at\ 12\ or\ 24\ months}{weight\ at\ baseline} \cdot 100 \quad (1)$$

Additionally, weight recurrence between months 12 and 24 was calculated as:

$$\%WeightRecurrence = \frac{weight\ at\ 24\ months - weight\ at\ 12\ months}{weight\ at\ 12\ months} \cdot 100 \quad (2)$$

The formula used the 12 month measurement as a proxy for the weight nadir. This pragmatic choice was dictated by the heterogeneous follow-up schedules across the included studies and is supported by evidence that most substantial weight loss after bariatric metabolic surgery occurs within the first year, after which the weight curve typically plateaus.[6,16] This approach maximized the number of patients eligible for inclusion in the weight regain sub-analysis.

In both formulas, outcomes were normalized to baseline values to capture proportional changes relative to initial conditions, thereby improving interpretability. Outcomes were then examined in relation to treatment type (RYGB vs SG) and potential predictors. To account for response heterogeneity across studies and potential confounding by baseline variables, we first considered an ANOVA including the "Study" factor and the "Study×Treatment" interaction term. ANCOVA was subsequently applied to also correct for differences in baseline conditions. To assess and compare outcome distributions, we applied kernel density estimation, a non-parametric method for estimating probability density functions. The 33rd and 67th percentiles of the 12 month %ΔWeight distribution were determined both overall and within each treatment group. A univariable multinomial logistic regression model was used to assess the association between treatment and weight loss categories identified by percentiles computed on the whole sample. Based on treatment specific percentiles, SG and RYGB patients were categorized into three groups to ensure a comparable number of patients within each group:

- Group 1: %ΔWeight $at\ 12\ months \leq$ 33rd percentile

- Group 2: 33rd percentile < %ΔWeight $at\ 12\ months \leq$ 67th percentile
- Group 3: %ΔWeight $at\ 12\ months$ > 67th percentile

The categorical variables were labeled %ΔWeightSG and %ΔWeightRYGB for SG and RYGB patients, respectively.

2.3 Prediction of 12 month percent weight loss

Factor analysis of mixed data (FAMD), clustering and Classification Neural Network

Anova was used to test for possible differences in basal characteristics among the three groups identified by the levels of the %ΔWeightSG and %ΔWeightRYGB variables. When differences arose, the underlying structure of relationships among all variables (both quantitative and qualitative) were explored by a Factor Analysis of Mixed Data (FAMD). FAMD combines Principal Component Analysis (PCA) for continuous variables and Multiple Correspondence Analysis (MCA) for categorical variables. Data interpretation was performed by analysing the squared loading plots, for both qualitative and quantitative variables, in the PCs space. Variables furthest from the origin have the highest squared loading values and therefore are more important in explaining the variance captured by the two dimensions characterizing the plane. Variables clustered near the origin are less correlated with the two dimensions. The factor loadings of quantitative variables on the PCs provide a measure of the correlations, that is of the information shared, between each variable and a given PC. To investigate whether an inherent structure exists within the observed data—such as the grouping of individuals based on specific characteristics—k-means clustering was then performed on the principal components (PCs) derived from the FAMD analysis and the Kullback-Leibler divergence was used to quantify the divergence between cluster distributions after having chosen one as reference. The variables included in the analysis were age, BMI, Waist Circumference, Diabetes status (Yes/No), basal glycemia, insulinemia, triglycerides, LDL-cholesterol, HDL-cholesterol, total cholesterol and HOMA-IR.

The association between the derived clusters and the qualitative variables was assessed using a Chi-Squared test. The Analysis of Variance (ANOVA) was used to assess if there were differences in quantitative variables among clusters. Tukey's 'Honest Significant Difference' method was used for post-hoc pairwise comparisons.

A classification Neural Network (NN) model, including the FAMD cluster membership, was then employed to test the ability of patient baseline characteristics in predicting 12 month weight loss classified according to the definitions above. The Receiver Operating Characteristic (ROC) curve was used to measure the classification performance of the NN model. The One-vs-Rest (OvR) approach was used for computing the ROCs treating each class as a binary classification problem. Results were reported in terms of Area Under the Curve with the relative 95% confidence intervals. The analysis only included individuals with no missing values on the considered variable subset.

To optimize the neural network, we tuned two hyperparameters: the number of hidden units (size) and the weight decay (decay). A bootstrap resampling strategy was applied using the trainControl function of the caret R package, which generated 100 resampled datasets by randomly sampling 70% of the training data with replacement. At each iteration, the network was trained on the resampled dataset and evaluated on the corresponding out-of-bag samples. This iterative procedure yielded robust performance estimates across a predefined grid of size and decay values. The bestTune parameters were selected as those producing the highest accuracy for the subsequent analysis.

The final model architecture consisted of input nodes representing the predictors, a set of hidden nodes and bias nodes determined during tuning, and three output nodes corresponding to the weight loss categories. Connections between layers are represented by weighted edges.

2.4 Modelling of the normalized weight trajectories up to 24 month follow up

All individuals with four or more time points up to 24 month follow-up after bariatric metabolic surgery were analysed to identify weight trajectory patterns. The ultimate goal was to identify potential predictors of different trajectories and mid-term treatment response. To this end, at each time point t (the follow-up visit), normalized weights, calculated as weight at time t divided by pre-surgery weight (time 0, before treatment), were computed and modelled using the following procedure:

1) for each individual, the calculated normalized weights (NWeights) over time were fitted using the following two models:

$$NWeights = 1 - \delta \left(1 - \frac{1}{1 + (\frac{t}{k})^{\gamma}}\right) \quad (3)$$

$$NWeights = e^{-\lambda_1 t} + \delta \left(1 - e^{-\lambda_2 t}\right) \quad (4)$$

These two models were used to represent two distinct weight loss trends:

- Sustained weight loss: individuals who successfully lost weight and maintained the weight loss throughout the observation period.
- weight loss with final weight recurrence: individuals who initially lost weight but later regained some or all of it during the observation period.

In the first model, hereafter referred to as the “Hill” model due to its similarity to a decreasing “Hill” function, the parameter δ regulates the magnitude of the normalized weight decrease. Larger values of δ correspond to greater proportional changes in post-treatment weight. The parameter k represents the time point at which the normalized weight is reduced by δ /2. The parameter γ governs the rate at which the normalized weight approaches its minimum.

In the second model, named the “Two-exponential” model being a mixture of two exponential functions, the parameter δ represents the equilibrium point toward which the normalized weight tends after an initial weight loss and subsequent recurrence. The parameters λ_1 and λ_2 represent the rates of weight loss and recurrence, respectively, with $\lambda_1 > \lambda_2$.

For each subject, the normalized weight trajectory over the 24 month period was modelled using the model that minimized the loss function when fitted to the observed data. The loss function is defined as:

$$loss = \sum_{i=1}^{n} \left(\widehat{\mathrm{NWeights}}_i - \mathrm{NWeights}_i\right)^2 \quad (5)$$

where $\widehat{\mathrm{NWeights}}_i$ is the predicted normalized weight at the i-th month, $\mathrm{NWeights}_i$ is the observed normalized weight at the same time point and n is the number of observations.

2) After calculating the loss values for each model and subject, patients were categorized into two groups: those whose weight trajectories were better represented by the “Hill” model and those whose trajectories were better explained by the “Two-exponential” model.

For each of the two groups (“Hill” and “Two-exponential”) and for each surgical procedure (RYGB and Sleeve Gastrectomy), a separate k-means longitudinal clustering procedure was applied to the predicted curves to identify clusters of distinct NWeight trends over time.

3) To identify the population parameters characterizing each cluster a mixed effects model was used and population estimates of the three model parameters (δ, γ, k for the "Hill" model and δ, λ_1, λ_2 for the "Two-exponential" model) within each cluster were obtained.
4) To explore the specific characteristics of each cluster, baseline variables were analysed. ANOVA and chi-squared tests were employed to examine differences in continuous variables among longitudinal clusters, as well as to assess associations between cluster membership and categorical factors. Due to variations in the data collected across different studies, a subset of common, highly relevant baseline variables was selected. This subset included: age, gender, BMI, waist circumference, baseline glycemia and insulinemia, HOMA-IR, glycated haemoglobin, diabetes status, LDL-cholesterol, HDL- cholesterol, total-cholesterol, and triglycerides.
5) Baseline characteristics were evaluated as potential predictors of binary clustering membership, categorized by the two trajectory types: sustained weight loss and weight loss with recurrence. A Neural Network classification model was employed for this analysis.

All analyses were performed using R Statistical Software Results[17], while the fitting procedure was performed in Julia.[18] Predictive models were trained on a designated training set and validated on an independent testing set. The dataset was partitioned using the *createDataPartition* function from the caret R package, which applies stratified random sampling to preserve class distributions across subsets. This approach ensured that the relative proportions of outcome classes in the original dataset were maintained in both the training and testing samples, thereby reducing the risk of sampling bias.

3. RESULTS

Figure 1 presents the estimated distribution of %ΔWeight using kernel density estimation for bariatric metabolic surgery overall (Panel A) and by treatment at 12 and 24 month follow-ups (Panels B and C, respectively). Figure S1 shows the same information for the absolute weight loss (ΔWeight). The estimated kernel density of %WeightRecurrence by treatment is shown in Panel D. RYGB exhibited unimodal distributions for both percent weight loss and weight recurrence, whereas SG showed bimodal distributions. At the 12 month follow-up, patients were stratified into three equal groups based on weight loss: one-third lost less than 24.2% of their baseline weight, one-third achieved between 24.2% and 33%, and the remaining third exceeded a 33% reduction (see the table in Figure 1). The association between treatment and weight loss quantile classes was significant ($P<0.0001$). Among those who lost less than 24.2% of their initial weight, 58% had undergone SG, whereas among those who lost more than 33%, 66% had undergone RYGB. The univariable multinomial logistic regression model using the first tertile (weight loss <24.2%) as the reference group showed that transitioning from RYGB to SG significantly decreased the odds of belonging to the second tertile (24.2–33% weight loss) by 1.07 ± 0.18 log-odds units ($P<0.0001$), and decreased the odds of being in the third tertile (>33% weight loss) by 0.98 ± 0.18 log-odds units ($P<0.0001$). These values correspond to odds ratios of 0.34 and 0.37, respectively, indicating substantially lower odds of greater weight loss for SG compared to RYGB. SG resulted in fact in lower percent weight loss, with the 33rd percentile at 18% and the 67th percentile at 31%, while RYGB led to significantly greater weight loss, with percentiles around 26% and 35%. The mean percent weight loss at 12 months was $30.3 \pm 8.2\%$ after RYGB and $25.4 \pm 10.8\%$ after SG ($P<0.001$). The ANOVA, which included the "study" factor and the "study×treatment" interaction, confirmed the presence of response heterogeneity across the studies and suggested that study context acts as a confounding factor. Despite this variability, the subsequent analysis of contrasts between the estimated marginal means consistently highlights that RYGB produces a greater average percent weight loss at 12 months than SG. Specifically, pairwise comparisons between the two treatments within each of the five studies (including both RYGB and SG patients) revealed that in three cases, the RYGB-SG contrast was significantly greater than zero (3.64±1.49%, P=0.0149; 12.40±1.01%, P<0.001; 7.40±1.22%, P<0.001). In the two remaining studies where the difference did not reach statistical significance, the contrast remained positive (1.94±1.62, P=0.23 and 2.34±1.73%, P=0.17), underscoring that RYGB consistently yielded a larger average weight loss in every study. Similar results were obtained when evaluating the effect of the treatment on delta weight, adjusting also for baseline variables in the subset of individuals with complete covariate data. The only significant basal covariates were BMI, age and gender.

~~while~~ At 24 months ~~it~~ percent weight loss was 26.3 ± 11.3% for RYGB and 21.4 ± 11.6% for SG (P<0.001). Percent weight recurrence relative to weight reached at 12 months was higher in RYGB but was not significantly different between the two groups (2.2 ± 8.9% in RYGB vs. 0.7 ± 6.4% in SG, P=0.069).

Since RYGB demonstrated superior weight loss outcomes compared to SG, we further analysed individual characteristics that might influence treatment response separately for each procedure. Patients were classified into three groups based on their weight loss at 12 months, using the 33rd and 67th percentiles as cutoffs to maintain balance. Low responders were defined as those achieving ≤18% weight loss following SG or ≤26% after RYGB, while high responders exceeded 30% weight loss for SG and >35% for RYGB, with intermediate responders falling between these thresholds. This classification allowed us to identify key factors influencing surgical outcomes, providing insight into factors contributing to the variability in weight loss success after bariatric metabolic surgery. In the following sections, these three-level variables are referred to as %ΔWeightSG and %ΔWeightRYGB.

3.1 Factors influencing Percent Weight Loss at 12 month Follow-Up

A sub-sample of 619 patients (381 RYGB and 238 SG) with complete baseline data was analyzed to examine the association between initial characteristics and weight loss outcomes at 12 months after surgery. Baseline characteristics are presented in Table S1, stratified by percentile cutoffs approximated to 25% and 33% to create clinically interpretable categories. Table S2 reports the P values from post hoc pairwise comparisons between these categories. Table 1 presents the means and standard deviations (or percentages for categorical variables) of predictive factors overall and in the two treatment groups, along with P values from independent t-tests. Gender distribution did not differ significantly between procedures (P=0.252), whereas diabetes prevalence was notably higher in the RYGB group (66.40%) compared to the SG group (44.11%, P<0.001). Patients undergoing RYGB also exhibited significantly higher baseline BMI, glycemia, and insulin resistance (HOMA-IR) (P<0.001, P=0.014, and P=0.006, respectively).

Univariate ANOVAs were used to assess differences in baseline characteristics across the three weight loss quantile classes, with treatment and the treatment-by-class interaction included as between-subjects factors. Age, BMI, fasting glucose, triglycerides, and total cholesterol varied significantly among the classes and were also influenced by treatment and its interaction with class. These findings warranted stratified analyses within each treatment group to explore how baseline characteristics might predict individual treatment responses.

3.1.1 Sleeve Gastrectomy

Table 2 provides a descriptive analysis of patients stratified by weight loss response percentiles (approximated to more clinically significant thresholds) following SG. Significant differences (all Ps<0.001) were observed across groups for age, baseline BMI, glycemia, total cholesterol, and triglycerides, with lower values in patients exceeding the 67th percentile of weight loss, except for BMI, which was higher in this group. Waist circumference showed higher mean value in the intermediate weight loss group (P=0.040), while HOMA-IR was lower in patients with greater weight loss but did not reach statistical significance (P=0.09). Table S3 presents P values for post-hoc pairwise comparisons, where differences between the lowest and highest weight loss groups were highly significant. Intermediate responders showed significantly lower baseline glycemia and triglycerides compared to low responders, while high responders were younger and had a higher BMI than intermediate responders (P=0.008 and P=0.016, respectively). Gender and diabetes status were also significantly associated with weight loss classification (P=0.014 and P<0.001, respectively). Notably, diabetes was present in 73% of low responders but only 16% of high responders.

Weight loss at 12 and 24 months was strongly correlated (P<0.0001). Among those who lost more than 30% of their baseline weight at 12 months, 77% maintained this reduction at 24 months. Conversely, 74% of those with less than 18% weight loss at 12 months showed no further improvement. The %WeightRecurrence variable did not differ significantly between groups, with mean values of -0.1±6.5% (low responders), 1.2±5.6% (intermediate responders), and 3.7±7.3% (high responders).

To further explore individual variability in treatment response, a Factor Analysis of Mixed Data (FAMD) was conducted, reducing dataset complexity and identifying clusters of patients with shared baseline characteristics. Variables included in the analysis were selected based on an ANOVA threshold of P≤0.10. The sample (n=238) was randomly divided into training (n=169) and validation (n=69) sets, ensuring balance for %ΔWeightSG. The scree plot (Figure S2, Panel A) indicated that the first four principal components explained most of the variance, together accounting for 72% (Figure S2, Panel B). Figure S3 provides squared loading plots and factor loadings for these dimensions.

The first dimension was primarily driven by total cholesterol, diabetes status, baseline glycemia, triglycerides, LDL-cholesterol, and HOMA-IR, all positively correlated with the component, highlighting a poor metabolic and lipid profile for high values of the dimension. The second dimension was influenced by waist circumference, gender, and HOMA-IR, with higher values observed in men and those with insulin resistance. The third dimension was strongly positively associated with LDL cholesterol, total cholesterol, and waist circumference (Figure S4).

Cluster analysis identified three distinct patient groups (Figure 2, Panels A-C):

Cluster 1 (low values on both first two dimensions): Comprised entirely of women (100%), with a relatively healthier metabolic and lipid profile. Only 28% had diabetes, and they achieved the greatest weight loss post-surgery.

Cluster 2 (low values on the first dimension, high on the second): Comprised exclusively of men with high waist circumference.

Cluster 3 (high values on the first dimension): Characterized by a poor metabolic and lipid profile, with diabetes present in 94.7% of cases.

The Kullback-Leibler divergence, which measures the divergence between probability distributions (using Cluster 3 as the reference), was 4.7 for Cluster 1 and 5.6 for Cluster 2. Table S4 reports baseline characteristics by cluster, while Table S5 provides pairwise comparisons. Weight loss at 12 months differed significantly among clusters ($P<0.0001$): Cluster 1 achieved the highest weight reduction (28.2±11.8%), followed by Cluster 2 (26.0±10.7%) and Cluster 3 (16.5±5.1%). Pairwise comparisons confirmed highly significant differences between Clusters 1 vs. 3 and Clusters 2 vs. 3 ($P<0.0001$). The association between %ΔWeightSG and clustering was also significant ($P<0.0001$), with 74.5% of Cluster 3 classified as low responders (%ΔWeight ≤18%) and only 4.2% achieving >30% weight loss.

A Neural Network (NN) analysis incorporating baseline characteristics and FAMD cluster membership was used to predict %ΔWeightSG response categories. Figure 2, Panel D presents NN structure on the training dataset, achieving an overall accuracy of 70.4%, with sensitivities of 83.3% for low responders, 33.3% for intermediate responders, and 84.5% for high responders. Validation accuracy was 72.5%, with sensitivities of 81.5%, 38.9%, and 87.5%, respectively. While intermediate response prediction remained a challenge, the model performed well in identifying extreme outcomes. Figure 2, Panel E displays ROC curves using a One-vs-Rest (OvR) approach to assess NN classification performance.

3.1.2 Roux-en-Y Gastric Bypass

Table 3 reports the descriptives according to the percentile cut-offs (approximated to 26% and 35% of weight loss). The only significant variables were age (P=0.0067), BMI (P=0.0018), gender (P=0.006) and diabetes status (P=<0.0001). Patients who experienced the largest weight reduction were younger, had a larger BMI, were for 60% females. Of patients with diabetes, the 25% were in this group, while the 39% were in the group who had the lowest weight loss. Table S6 reports the pairwise comparisons between each couple of classes. Of patients who achieved a weight loss greater than 35% at 12 months, 62% maintained this percentage of loss at 24 months, while 84% of those with 12 months weight loss less than 26% showed no further improvement by month 24. Of patients with initial intermediate weight loss, 31.6% passed to the inferior category at 24 months, regaining weight, and only 14.5% improved passing to the category %ΔWeight>35%. Association between the two three-level variables (%ΔWeightRYGB at 12 and 24 month follow-up) was significant (P<0.0001). Any statistical model trying to predict treatment response at 12 months based on the above baseline characteristics is insufficient to accurately classify RYGB patients in the three classes of percent weight loss.

Therefore, we tried to understand if there were any relationships between basal conditions and 24 month follow-up response to treatment or weight recurrence. The subsequent analysis takes into consideration the weight trajectories up to 24 months after treatment for both SG and RYGB patients.

3.2 Modelling of the normalized weight trajectories

A total of 415 patients (130 SG and 285 RYGB) were included in the analysis of weight trajectory predictions up to 24 months after surgery. These are subjects with at least four observations during their follow-up and monitored for at least 12 months after surgery. In presence of a sufficient number of observations, predictions at the end of the follow-up could be estimated also in the case of missed 24 month weight measurement. Among the patients who underwent SG, 84 trajectories were better represented by the “Hill” model, while the remaining 46 were better fitted with the “Two-exponential” model. For those patients undergone RYGB, the corresponding numbers were 131 and 154, respectively.

3.2.1 Sleeve Gastrectomy

3.2.1.1 Longitudinal clustering

SG patient weight loss trajectories were clustered into two "Hill" model groups (moderate and substantial loss, no weight recurrence) and one "Two-Exponential" group. Figure 3 (Panels A-C) shows the individual weight loss trajectories within each cluster, while Panels E-H depict representative patient time courses.

3.2.1.2 Population-Level Weight Loss Estimation

A mixed-effects model was used to estimate population-level weight loss parameters. In the “Hill” model, the primary parameter δ, which characterizes final weight loss, was significantly higher in cluster 2 (0.24±0.016, P<0.0001) compared to cluster 1 (0.22 ± 0.010, P < 0.0001). The differential effect for parameter γ was -0.14 ± 0.07 (P = 0.04), while parameter k showed no significant differences between clusters. In the "Two-exponential" model, δ, the key parameter reflecting the normalized weight loss plateau, was estimated at 0.88 ± 0.005, translating into a final population-level weight loss estimate of 22% after subsequent weight recurrence. Detailed results for the SG group are available in Tables S7 and S8.

3.2.1.3 Baseline Characteristics and Longitudinal Clustering

Tables S9 and S10 present the baseline characteristics of the three identified trajectory groups and the pairwise post hoc comparisons, respectively. SG patients with sustained weight loss (group 2) were younger and had more favourable metabolic and lipid profiles. While groups 1 and 3 exhibited similar weight loss at 24 months, group 3 (weight recurrence) had on average higher HbA1c and cholesterol levels (P = 0.07 and P = 0.04, respectively) and significantly higher triglycerides (P = 0.019).

3.2.1.4 Treatment Response Prediction at 24 month Follow-Up

The association between %ΔWeightSG and longitudinal clustering was highly significant (P < 0.0001). All patients who achieved a %ΔWeight greater than 30% at 12 months were classified in cluster 2 ("Substantial and sustained weight loss"). Among those with intermediate weight loss (18%–30%), 52% fell into cluster 1 ("Moderate but sustained weight loss"), while the remaining 48% were evenly distributed between clusters 2 and 3. All individuals with %ΔWeight below 18% at 12 months were assigned to either cluster 1 or cluster 3. These findings suggest that high responders at 12 months either continued to lose weight or maintained their weight, whereas poor responders showed no significant improvement over time. Figure 4 (Panels A-C) illustrates the distribution of patients within longitudinal clusters based on their 12 month %ΔWeight, where green trajectories represent individuals with %ΔWeight greater than 30%, yellow trajectories correspond to those with weight loss between 18% and 30%, and red trajectories indicate patients with a poor response (%ΔWeight ≤18%).

3.2.2 *Roux-en-Y Gastric Bypass*

3.2.2.1 Longitudinal Clustering

In the RYGB group, two distinct clusters were identified among both the "Hill" and "Two-exponential" trajectories. The first cluster included individuals who achieved moderate mid-term weight loss, while the second cluster comprised those who experienced substantial weight reduction from their initial weight. Additionally, two more clusters (3 and 4) consisted of patients who initially lost a moderate or substantial amount of weight during the first post-surgical year but subsequently regained between 6% and 7% of their weight at the trough. Figure 5 (Panels A-D) presents the individual weight loss trajectories within each cluster, while Panels E-H depict representative patient time courses.

3.2.2.2 Population Model Parameter Estimates from Mixed-Effects Models

In the "Hill" model, the primary parameter δ was significantly higher among individuals who achieved greater weight loss. Specifically, δ was 0.29±0.008 in cluster 1, while the differential effect for cluster 2 was 0.17±0.012 ($P<0.0001$), indicating that patients in these two clusters reached significantly different final weights. Parameter k also differed significantly between clusters, with values of 4.03±0.134 in cluster 1 and a differential effect of 0.062±0.018 for cluster 2 ($P=0.004$).

For the "Two-exponential" model, δ was significantly lower in cluster 4, suggesting a smaller equilibrium weight after weight recurrence and a greater overall weight loss. The differential effect was -0.13±0.01 ($P<0.0001$). Detailed results are available in Tables S11 and S12.

3.2.2.3 Baseline Characteristics and Longitudinal Clustering

The univariable associations between longitudinal clustering and baseline characteristics (Tables S13–S14) reveal that patients with the highest sustained weight loss were significantly younger, had a higher BMI and larger waist circumference, and exhibited lower fasting glucose, insulin, and HOMA-IR levels, indicating reduced insulin resistance. They also had lower LDL- and total-cholesterol levels.

3.2.2.4 Treatment Response Prediction at 24 month Follow-Up

To further investigate weight-loss trajectories, RYGB patients were categorized based on their normalized weight loss trends. Table S15 presents the baseline characteristics of the two trajectory groups. Nearly all variables differed significantly between groups, except for baseline weight (P=0.24), age (P=0.10), and HDL-cholesterol (P=0.064). However, patients following "Hill" trajectories were, on average, younger (46.5±7.86 vs. 47.9±5.9). Baseline fasting glycemia, insulinemia, glycated hemoglobin, HOMA-IR, triglycerides, total cholesterol, and LDL-cholesterol were significantly elevated in individuals who regained weight. Conversely, BMI and waist circumference were lower in this group. Gender was not associated with trajectory type, but diabetes was more prevalent in those who regained weight (63% of individuals with diabetes followed the "Two-exponential" trend). These findings suggest that metabolic and anthropometric characteristics may be key factors of post-RYGB weight-loss patterns.

A neural network (NN) model was developed to predict weight-loss trajectories based on baseline characteristics. Given that diabetes was present in 90% of cases but had missing values, it was excluded as a predictor. Of the 285 patients, 251 had complete baseline data and were randomly divided into a training set (189 patients) and a validation set (62 patients).

In the training set, the model achieved 79% accuracy, correctly predicting "Hill" trends in 77% of cases and "Two-exponential" trends in 81%. In the validation set, accuracy was 74%, with correct predictions for "Hill" and "Two-exponential" trajectories in 70% and 78% of cases, respectively. Figure 6 shows the neural network architecture (Panel A) and the ROC curve (AUC = 82.8%, CI: 76.5–88.7, Panel B). Panel C visualizes individual trajectories classified into the two trajectory types, distinguishing between maintained weight loss and weight recurrence. Panel D illustrates the predicted trajectories within the validation set, with sky-blue shading representing the training set range, brown lines indicating average trends, and purple and gold shaded areas showing the 90% and 50% envelopes of predicted time courses.

3.2.2.5 Comparison of RYGB and SG Patients with Sustained Weight Loss

Patients categorized into the "Substantial sustained weight loss" trend for both SG and RYGB (Tables S9 and S13) were compared to evaluate baseline differences between the two surgical procedures. Significant differences were found for baseline weight, HbA1c, fasting insulin, fasting glucose, and HOMA-IR, all of which were higher in the RYGB group (see Table 4). This suggests that, even among patients with relatively young age and favourable lipid profiles, RYGB may be the preferred option for individuals exhibiting insulin resistance and impaired glucose metabolism.

4. DISCUSSION

In this study, we explored the variability in weight-loss outcomes among individuals who underwent bariatric metabolic surgery, focusing on high- and low-responders across the two most performed procedures: RYGB and SG. To achieve this, we employed both Factor Analysis of Mixed Data (FAMD) and Neural Network (NN) analysis, leveraging their complementary capabilities. FAMD was instrumental in reducing the complexity of the dataset while preserving interpretability, allowing us to identify clusters of individuals with similar characteristics. Neural networks built on these findings by capturing intricate, non-linear relationships between variables, enabling robust predictions of surgical outcomes. Together, these methods, applied to SG procedure, provided a dual advantage, combining exploratory insights with predictive accuracy, and enhancing the overall performance of our study.

The distribution of percentage weight loss among the participants revealed important trends. In patients undergoing RYGB, the distribution followed a unimodal pattern, while for SG, it was bimodal, reflecting distinct groups with varying weight-loss responses. Moreover, the weight loss distributions of SG were shifted towards lower values while the weight recurrence distributions are superimposed. The varying responses to treatment, reflected in the different weight loss percentiles between the two surgical procedures, led us to conduct two separate analyses. This decision was further supported by the observation that when patients were grouped into three classes based on the 33rd and 67th percentiles of percent weight loss (18% and 30% for the SG group, and 26% and 35% for the RYGB group), most baseline characteristics differed significantly within the SG group. In contrast, the baseline characteristics for RYGB showed no significant differences among the classes.

The FAMD analysis highlighted that metabolic status (dimension1) serves as the primary axis of patient variability in the FAMD model, suggesting that glycemic and lipid profiles are the dominant factors driving overall patient clustering, with anthropometric measures playing a secondary role in subsequent dimensions (waist circumference and gender driving the second dimension). Cluster analysis following FAMD analysis identified three different clusters in SG: The first cluster grouped younger women with healthier metabolic and lipid profiles, minimal diabetes prevalence, and with the most relevant weight loss. Patients in the second cluster were all men with elevated waist circumference. Their weight loss outcomes were moderate, positioned between the other two clusters. The third cluster comprised older individuals, most of whom with type 2 diabetes, insulin resistance, and hyperlipidemia. These patients achieved limited weight loss, generally not exceeding 20% of their baseline weight.

The neural network model demonstrated the ability to effectively differentiate between individuals who would achieve ≤18% weight loss (33rd percentile, with a sensitivity of 83.3% in the training and of 81.5% in the validation set) and those exceeding 30% (67th percentile, with sensitivity of 84.5% and 87.5% in the training and validation sets, respectively) weight loss at 12 months post-SG, using preoperative patient characteristics. While the prediction of intermediate response remains a challenge (resulting in a moderate overall accuracy of 70.4%), the model provides a valuable first step toward identifying potential high- and low-response patients, which holds significant clinical utility. These findings highlight the crucial role of age, metabolic factors, and lipid profiles in influencing treatment response in patients undergoing SG. For these patients, moreover, three distinct trends (longitudinal clustering) emerged from the weight loss trajectory analysis: moderate but sustained weight loss, substantial and sustained weight loss and moderate weight loss with subsequent weight recurrence. The strong association (P<0.0001) between percentile classes and longitudinal clustering highlights the predictive power of 12 month percent weight loss for mid-term weight loss trajectories. Early success in weight loss at 12 months is a strong indicator of sustained weight loss. Conversely, poor weight loss in the first year suggests a higher likelihood of continued challenges (see Figure 4). The intermediate group indicates that while some will have moderate success, others will have either sustained success, or rather poor results. The neural network (NN) model also exhibited a limited ability to predict the intermediate class with good sensitivity. This may be attributed to the influence of unmeasured confounders. Specifically, for individuals lacking a distinct metabolic and lipid profile, factors such as genetic predispositions (as variants located in candidate genes associated with obesity-related phenotypes, such as FTO[19], LEP, MC4R[20,21]), hormonal influences (like ghrelin and leptin[22]), lifestyle choices (dietary adherence or physical activity[23,24]), or psychological aspects (eating behaviour or mental health status[24]) could significantly impact their weight loss responses. The absence of this crucial information within our dataset represents a limitation of our study.

Although the influence of unmeasured factors limits the precision of outcome prediction in intermediate groups, the broader therapeutic landscape for obesity is rapidly evolving. Recent advances in pharmacotherapy are achieving degrees of weight loss that approach those traditionally observed with bariatric metabolic surgery. For example, in a randomized clinical trial, the triple GLP-1/GIP/glucagon receptor agonist retatrutide, administered at 12 mg daily, produced a ≥20% reduction in body weight in nearly two-thirds of participants, ≥25% reduction in half, and ≥30% reduction in one-quarter of the study population[25]. These results underscore the potential of next-generation agents to narrow the gap between medical and surgical interventions.

However, the efficacy of GLP-1 receptor agonists, as well as dual and triple incretin-based therapies, is substantially attenuated in individuals with type 2 diabetes.[26,27] This blunted response likely reflects underlying metabolic disturbances such as insulin resistance and impaired hormonal signaling. In contrast, bariatric metabolic surgery consistently produces weight reductions exceeding 20% even in patients with type 2 diabetes,[4–6] and uniquely confers the possibility of diabetes remission.[3,5] These effects highlight the enduring superiority of surgical approaches for durable metabolic improvements, particularly in populations with advanced metabolic disease.

RYGB consistently proved to be more effective than SG in achieving weight loss, with high responders defined as those losing at least 35% of their initial weight, while low responders were those losing less than 26%. However, except for BMI, age, gender and presence of diabetes, which differentiate the classes above, baseline characteristics do not seem to predict the 12 month outcome. The focus for RYGB, therefore, was on mid-term (24 months of follow-up) response. Our analysis identified four distinct weight-loss trajectories following RYGB, revealing four main patterns: a subset of patients with moderate but sustained weight loss, high responders experiencing sustained weight loss, moderate and substantial weight loss followed by partial weight recurrence. Most baseline characteristics are significantly different among the four patterns, highlighting that patients who lose more, maintaining their weight loss, are younger and with a better metabolic and lipid profile (Table S13). Baseline characteristics are predictive of weight recurrence. The NN model was able to classify correctly 77% of the "Hill" and 81% of the "Two-exponential" trends in the training set, with the two percentages being 70% and 78% in the validation set, respectively, with a moderate overall accuracy of 74%. Furthermore, a comparison of high responders (substantial and sustained weight loss) across the two surgical procedures revealed that, even among younger individuals with favourable lipid profiles, RYGB may be the preferred option for patients with insulin resistance and impaired glucose metabolism. While SG high responders have a good metabolic phenotype, the average insulin resistance of RYGB patients was high 5.6±4.3 (versus 3.0±1.6 in SG high responders) and 70% of them had type 2 diabetes.

This suggests that while both procedures can be effective, RYGB may offer enhanced metabolic benefits in individuals with underlying insulin resistance, potentially leading to more sustained weight loss and improved glycemic control. These findings underscore the importance of tailoring surgical approaches based on a patient's metabolic profile rather than solely on traditional demographic parameters.

However, it is essential to weigh both the short- and mid-term adverse effects of each procedure, as those associated with RYGB may be more severe. While SG is generally characterized by a lower peri-operative complication profile, RYGB carries distinctive long-term risks, including the development of internal hernias and marginal ulcers.[28,29]

Our findings highlight that baseline metabolic characteristics play a pivotal role in predicting weight-loss outcomes and the likelihood of weight recurrence after bariatric metabolic surgery. Insulin resistance, type 2 diabetes, and hyperlipidemia were associated with both reduced weight-loss success and a higher probability of regaining weight. In contrast, younger individuals with healthier metabolic profiles tended to achieve more substantial and sustained weight loss, even when starting with a higher BMI. By combining FAMD and NN analysis, we were able to provide a deeper understanding of the predictors of weight-loss variability and lay the groundwork for personalized approaches to bariatric metabolic surgery, tailoring interventions to individual metabolic profiles to improve outcomes.

In conclusion, younger patients with preserved insulin sensitivity, normal glucose, and a favorable lipid profile achieved the most durable weight loss with minimal regain at two years. RYGB was more effective than SG, including in patients with type 2 diabetes and adverse metabolic profiles, and remains superior to currently available or investigational weight-loss drugs. However, it is to note that due to the scarcity of follow-up time points reported across the studies, the computation of weight recurrence relied on measurements at 12 and 24 months. While the inclusion of 18-month measurements would have potentially offered a more robust estimate of weight recurrence, such data were consistently absent across the included studies. This lack of intermediate data limits our ability to precisely track the true nadir. Future clinical studies on weight management interventions should standardize follow-up schedules to include the 18-month time point to enable more robust analyses of long-term weight maintenance and recurrence.

Interpretation of these findings must consider the heterogeneity of the pooled cohort, drawn from seven RCTs with varying inclusion criteria and follow-up durations. While this design introduces potential selection bias, it enhances external validity by reflecting the diversity of patients seen in clinical practice. Moreover, we acknowledge that data aggregation also introduces an inherent methodological heterogeneity related to laboratory protocols and surgical performance. Specifically, it was not possible to standardize the analytical techniques and assay kits used to measure key laboratories parameters, such as insulinemia, glucose, cholesterol, etc. across the different study centres. This variation constitutes a potential limitation. Moreover, statistical analysis demonstrated that the "study" variable and the interaction treatment/study were significant predictors of weight change (indicating a heterogeneity across studies). However, after correction by study and interaction, the overall effect size of the treatment on weight change remained highly significant and substantially consistent across studies. The agreement in the direction of the main effect suggests that the possible variation in surgical performance did not compromise the fundamental validity of our conclusion about the treatment's impact, justifying the decision to conduct separate analyses for the determination of individual phenotypes to better understand the response.

Moreover, it is to be noted that the reduced sample size beyond 12 months reflects differing study designs rather than attrition, limiting conclusions on longer-term outcomes.

Our analysis identified distinct phenotypes and predictive models for weight loss and regain. RYGB provided the greatest benefit in metabolically adverse phenotypes, whereas low-risk patients achieved durable outcomes with either procedure. These insights support the use of phenotype-based strategies to optimize personalized treatment selection.

Table 1. Baseline characteristics stratified by treatment and overall, along with 12 and 24 month follow-up percent delta weight and percent weight recurrence. P values are from independent t-test for continuous variables and Chi-Squared test for categorical variables.

	SG (238)	RYGB (381)	Overall (619)	
Continuous Variables	**Mean±SD**	**Mean±SD**	**Mean±SD**	**P value**
Age [years]	46.82±8.91	47.58±7.44	47.28±8.04	0.272
BMI [kg/m^2]	41.52±4.14	42.89±4.55	42.36±4.44	<0.001
Weight [kg]	117.49±17.44	125.11±18.88	122.18±18.69	<0.001
Waist circumference [cm]	134.23±22.19	137.74±23.22	136.39±22.87	0.06
Fasting plasma insulin [mU/ml]	25.28±16.21	26.78±15.69	26.2±15.89	0.25
Fasting plasma glucose [mmol/l]	6.47±2.44	7.02±3.05	6.81±2.84	0.014
Fasting plasma LDL-Cholesterol [mmol/l]	3.19±0.92	3.23±1.02	3.21±0.98	0.64
Fasting plasma HDL-Cholesterol [mmol/l]	1.21±0.38	1.24±0.36	1.23±0.36	0.33
Fasting plasma Triglycerides [mmol/l]	1.95±1.05	2.1±1.19	2.05±1.14	0.095
Fasting plasma Total Cholesterol [mmol/l]	5.27±1.05	5.43±1.16	5.37±1.12	0.078
HOMA-IR [mU/ml × mmo/L]	7.22±5.44	8.59±6.84	8.06±6.37	0.006
12 month %ΔWeight [%]	24.42±11.07	30.03±7.99	27.88±9.68	<0.001
24 month %ΔWeight* [%]	21.43±11.55	26.29±11.33	24.76±11.61	<0.001
%WeightRecurrence** [%]	0.68±6.38	2.18±8.91	1.73±8.25	0.069
Dichotomic Variables	**N (%)**	**N (%)**	**N (%)**	**P value**
Gender (Male) [#, (%)]	93 (39.08)	168 (44.09)	261 (42.16)	0.252
Presence of diabetes [#, (%)]	105 (44.11)	253 (66.40)	358 (57.83)	<0.001

*Sample size: N=400
**Sample size: N=367

Table 2. Baseline characteristics of the SG patients by classes identified by 33^{rd} and 67^{th} percentile of the %ΔWeight variable, along with 12 and 24 month follow-up percent delta weight and percent weight recurrence. P values are from Anova and Chi-Squared test for categorical variables.

Continuous Variables	**≤ 33th percentile (%ΔWeight≤18%) (n=93)**	**33th-67th percentile (18<3%ΔWeight ≤30%) (n=63)**	**>67th percentile (%ΔWeight >30%) (n=82)**	**P value**
Age [years]	49.62±6.96	47.43±9.39	43.16±9.32	<0.001
BMI [kg/m^2]	40.61±3.92	41.04±4.04	42.92±4.13	<0.001
Waist circumference [cm]	130.04±18.29	138.87±25.4	135.41±22.99	0.04
Fasting plasma insulin [mU/ml]	25.38±14.33	24.27±17.95	25.95±16.96	0.82
Fasting plasma glucose [mmol/l]	7.33±3.15	6.34±2.03	5.6±1.15	<0.001
Fasting plasma LDL- Cholesterol [mmol/l]	3.29±0.92	3.22±1.06	3.06±0.81	0.25
Fasting plasma HDL- Cholesterol [mmol/l]	1.19±0.25	1.2±0.29	1.24±0.53	0.60
Fasting plasma Triglycerides [mmol/l]	2.43±1.16	1.65±0.85	1.64±0.85	<0.001
Fasting plasma Total Cholesterol [mmol/l]	5.57±0.99	5.18±1.28	4.99±0.81	<0.001
HOMA-IR [mU/ml × mmo/L]	8.17±5.77	6.79±6.23	6.47±4.16	0.09
12 month %ΔWeight [%]	13.62±3.62	23.23±3.51	37.59±4.82	<0.001
24 month %ΔWeight* [%]	14.52±6.19	19.68±6.06	37.20±7.83	<0.001
%WeightRecurrence* [%]	-0.14±6.50	1.18±5.62	3.68±7.25	0.25
Dichotomic Variables	**N (%)**	**N (%)**	**N (%)**	**P value**
Gender (Male) [#, (%)]	40 (43%)	31 (49%)	22 (27%)	0.014
Presence of diabetes [#, (%)]	68 (73%)	21 (33%)	16 (19%)	<0.001

*Sample size: N=90

Table 3. Baseline characteristics of the RYGB patients by classes identified by 33rd and 67th percentile, along with 12 and 24 month follow-up percent delta weight and percent weight recurrence. P values are from Anova and Chi-Squared test for categorical variables.

Continuous Variables	**≤ 33th percentile (%ΔWeight ≤26%) (n=120)**	**33th-67th percentile (26<%ΔWeight≤35%) (n=150)**	**>67th percentile (%ΔWeight>35%) (n=111)**	**P value**
Age [years]	48.59±6.93	48.13±7.3	45.72±7.89	0.0067
BMI [kg/m^2]	42.3±4.45	42.41±4.23	44.18±4.85	0.0018
Waist circumference [cm]	137.97±20.7	135.53±24.66	140.48±23.67	0.2332
Fasting plasma insulin [mU/ml]	26.6±15.66	28.31±17.76	24.91±12.28	0.2203
Fasting plasma glucose [mmol/l]	7.21±2.95	6.91±3.18	6.97±2.98	0.7036
Fasting plasma LDL- Cholesterol [mmol/l]	3.16±1.05	3.31±1.04	3.19±0.94	0.4056
Fasting plasma HDL-Cholesterol [mmol/l]	1.27±0.38	1.23±0.3	1.22±0.4	0.5234
Fasting plasma Triglycerides [mmol/l]	2.25±1.22	2.05±1.11	2.02±1.25	0.2592
Fasting plasma Total Cholesterol [mmol/l]	5.44±1.18	5.47±1.2	5.36±1.09	0.769
HOMA-IR [mU/ml × mmo/L]	8.69±6.76	9.03±7.74	7.87±5.5	0.3913
12 month %ΔWeight [%]	21.08±4.11	30.10±5.55	39.62±3.66	<0.001
24 month %ΔWeight* [%]	19.31±7.16	28.50±6.78	37.54±7.62	<0.001
%WeightRecurrence* [%]	1.87±7.12	2.23±9.02	2.62±11.92	0.894
Dichotomic Variables	**N (%)**	**N (%)**	**N (%)**	**P value**
Gender (Male) [#, (%)]	67 (55.8%)	56 (37.3%)	45 (40.5%)	0.006
Presence of diabetes [#, (%)]	98 (81.7%)	92 (61.3%)	63 (56.8%)	<0.0001

*Sample size: N=216

Table 4. Baseline characteristics by treatment for individuals belonging to the "Substantial sustained weight loss" longitudinal cluster.

Continuous Variables	**SG (N=35)**	**RYGB (N=63)**	**P value**
Age [years]	44.17±9.32	44.21±8.11	0.983
Weight [kg]	118.61±15.87	127.17±18.81	0.025
BMI [kg/m^2]	43.23±3.76	44.23±4.85	0.289
Waist Circumference [cm]	132.17±20.43	136.08±18.8	0.341
HbA1c [%]	5.62±0.27	6.14±1.19	0.009
Fasting plasma Insulin [mU/ml]	13.26±6.85	21.33±13.75	<0.001
Fasting plasma glucose [mmol/l]	4.99±0.55	5.76±2.27	0.012
Fasting plasma LDL-Cholesterol [mmol/l]	2.91±0.94	2.96±0.8	0.806
Fasting plasma HDL- Cholesterol [mmol/l]	1.29±0.34	1.23±0.29	0.367
Fasting plasma Triglycerides [mmol/l]	1.66±1.03	1.9±1.45	0.333
Fasting plasma Total Cholesterol [mmol/l]	5.08±0.98	5.15±1.22	0.768
HOMA-IR [mU/ml × mmo/l]	2.97±1.61	5.59±4.27	<0.001
Dichotomic Variables	**%**	**%**	**P value**
Gender (Male) [%]	22.9	44.4	0.057
Presence of diabetes [%]	20	70.2	<0.001

Figure Legend

Figure 1. %ΔWeight (percent weight loss with respect to basal weight) distribution (kernel density estimation) at 12 month follow up for the whole sample (Panel A) and by treatment (Panel B). %ΔWeight at 24 month follow-up (Panel C) by treatment; %WeightRecurrence (percent weight recurrence with respect to weight reached at 12 month follow-up) distribution by treatment (Panel D). Below a table reporting the 33^{th}, 50^{th}, and 67^{th} percentile of %ΔWeight variable, overall and by treatment. Continuous and dashed vertical lines represent average values for SG and RYGB procedure, respectively.

Figure 2. Scatter plots of individual scores from FAMD analysis after clustering: 2D scatter plot on dimension 1 and dimension 2 (panel A), on dimension 3 and dimension 4 (panel B) and 3D scatter plot on dimension 1, 2 and 3 (panel C) for the SG group. Points are coloured and shaped according to their assigned cluster (Cluster 1, Cluster 2, or Cluster 3). The ellipses in panels A and B represent the convex hull (the smallest convex set that completely contains a given set of points) defining the boundary of each cluster, and the larger points are the centroid (mean) of each cluster.

Panels D and E show the results from the NN analysis for prediction of the three-level variable: %ΔWeight ≤18%, 18<%ΔWeight ≤30%, %ΔWeight>30% for the SG patients. Panel D: architecture of the neural network used in the analysis; in the training sample along with the area under the curves (AUCs) and the relative confidence intervals.

Figure 3. Panels A and B show the estimated weight trajectories with the "Hill" model (Moderate and Substantial sustained weight loss trends) while Panel C shows the estimated weight trajectories with the "Two-exponential" model (Moderate weight loss+final weight

recurrence) for the Sleeve Gastrectomy patients. Grey lines are used for individual estimated trajectories, black lines represent the average trend and blue lines are the 5th and 95th percentile trend. Panels D-F: observed normalized weights (black dots) and estimated curves (solid red lines) for three representative individuals from each of the three clusters.

Figure 4. SG Patients trends distributed in the longitudinal clusters (panels A-C) coloured according to the value of their 12 month %ΔWeight: green trajectories identify patients with 12 month %ΔWeight>30%; yellow trajectories identify patients with 12 month %ΔWeight between 18% and 30% and red trajectories identify patients with 12 month %ΔWeight≤18.

Figure 5. Panels A and B show the estimated weight trajectories with the “Hill” model (Moderate and Substantial sustained weight loss trends) while Panels C and D show the estimated weight trajectories with the “Two-exponential” model (Moderate and Substantial weight loss+final weight recurrence) for RYGB patients. Grey lines are used for individual estimated trajectories, black lines represent the average trend and blue lines are the 5th and 95th percentile trend. Panel E-F: Observed normalized weights (black dots) and estimated curves (solid red lines) for four representative individuals from each of the four clusters.

Figure 6. Panels A and B show the results from the NN analysis for prediction of the binary classification “Hill” vs “Two-exponential” trend for the RYGB patients. Panel A: architecture of the NN used. Panel B: ROC curve associate to the NN model in the training sample along with the area under the curve (AUC) and the relative confidence interval. Panel C: individual trends when grouped according to the two different trends (“Hill” vs “Two-exponential”),

distinguishing between maintained weight loss trajectories and weight loss with final weight recurrence trajectories. Panel D: sky-blue shaded area shows the range within which the training trajectories lie; brown lines represent the average trend of the patients belonging to the validation set according to their predicted group by the NN model; purple and gold shaded areas represent the 90% and 50% envelop of time courses of individuals in the validation sample as predicted by the NN model in the two trend groups.

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Author contributions

SP and GM: study conceptualisation and investigation methodology; GM: project administration and supervision; SR, DT: data curation, SP: formal analysis, validation and visualization, SP and MP: software generation; SP and GM: writing – original draft. All authors contributed to review & editing the manuscript.

Conflict of interest

G.M. has received consulting fees from Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Johnson & Johnson, Medtronic, Fractyl Inc., and Recor Inc. She also serves as a Scientific Advisor for Keyron Ltd, Metadeq Inc., GHP Scientific Ltd, and Jemyll Ltd. G.A. has received consulting fees from Metadeq Inc.

C.W.l.R. has received grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board. He serves on advisory boards for Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Sanofi Aventis, AstraZeneca, Janssen, Bristol-Myers Squibb, Glia, and Boehringer Ingelheim. Additionally, he is a member of the Irish Society for Nutrition and Metabolism, unrelated to the work presented here. P.N.N. has received grant and research support from Novo Nordisk and consulting fees from Aligos, AstraZeneca, Boehringer Ingelheim, Sagimet, Madrigal, Novo Nordisk, Shionogi, Zydus Therapeutics, and 89 Bio. He is also a member of the speakers' bureau for Eli Lilly, Echosens, Ipsen, and Novo Nordisk. I.B. is a consultant for Apollo Endosurgery, Boston Scientific, Nitinotes, Pentax, Cook Medical, Microtech, ERBE, Siemens, Myka Labs, and Endo Tools

Therapeutics S.A. and serves as a scientific advisory board member for Nitinotes, Myka Labs and Surgery. He performs sponsored lectures for Apollo Endosurgery, Boston Scientific, Cook Medical, and Microtech. Additionally, he has received research grants from Apollo Endosurgery, Endo Tool Therapeutics, and ERBE. A.G. has served as a consultant for: Boehringer Ingelheim, Eli Lilly and Company, Metadeq Diagnostics and Fractyl Health; has participated in advisory boards for: Boehringer Ingelheim, Merck Sharp & Dohme, Novo Nordisk, Metadeq Diagnostics, Pfizer and Regeneron. She has received speaker's honorarium and other fees from Eli Lilly and Company, Merck Sharp & Dohme, and Novo Nordisk, Pfizer.

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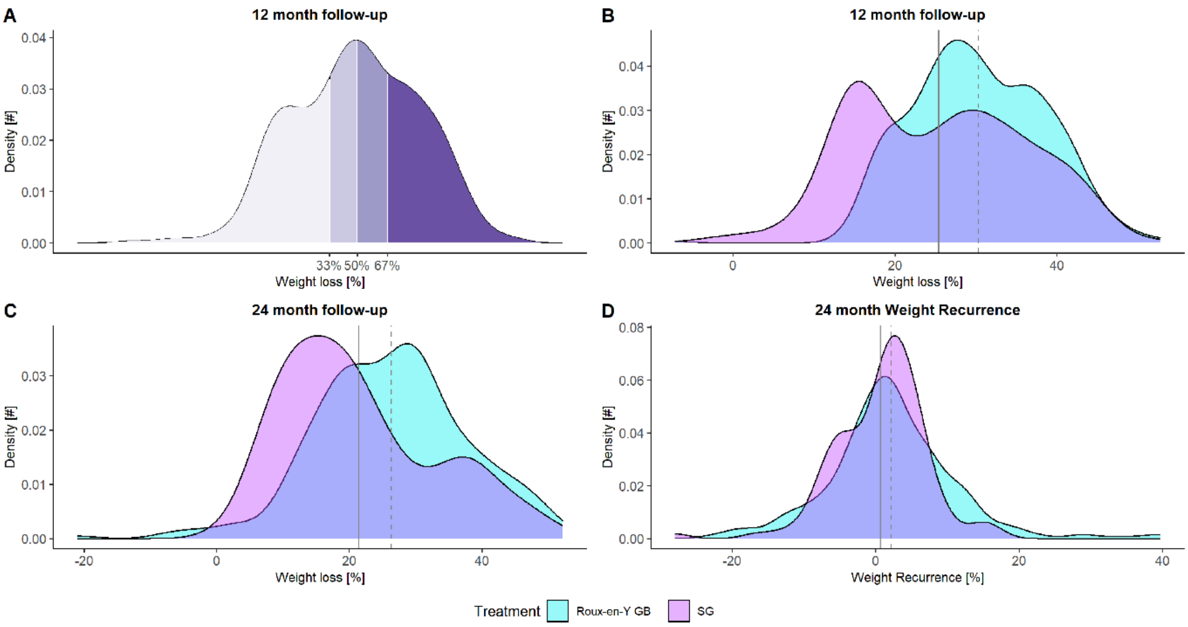
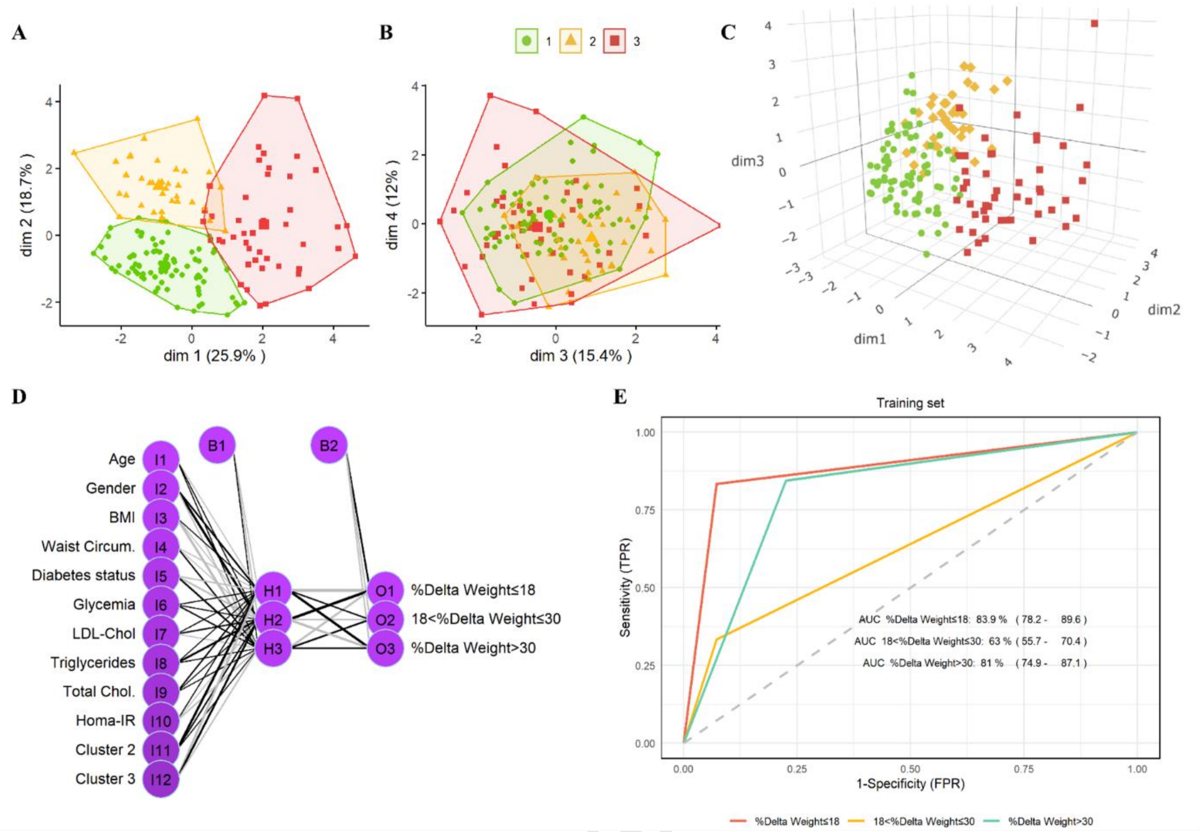
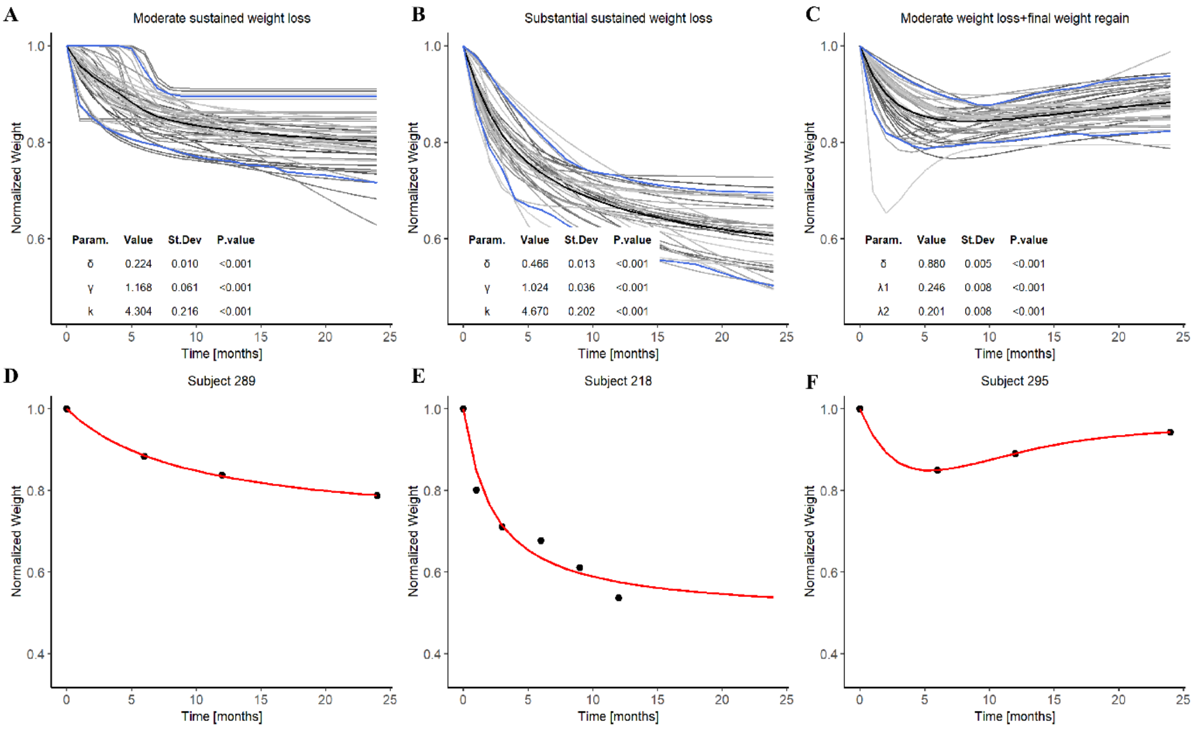
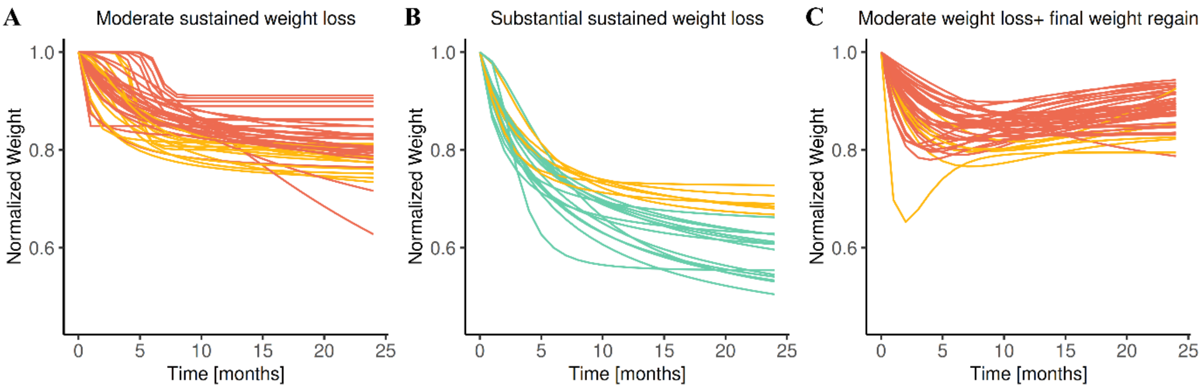


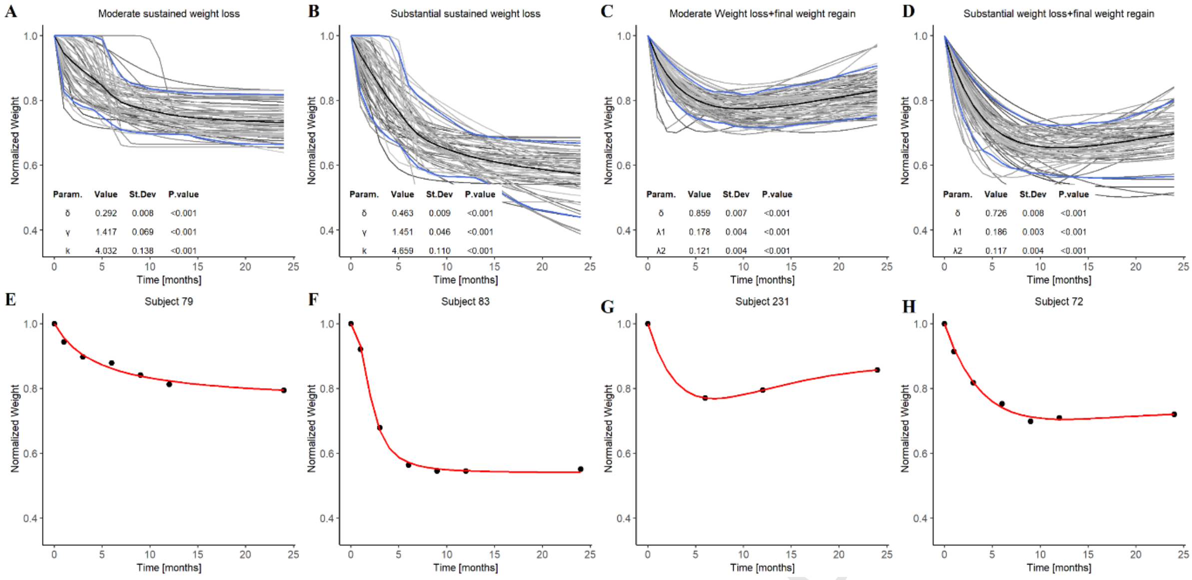
12 month %ΔWeight percentiles

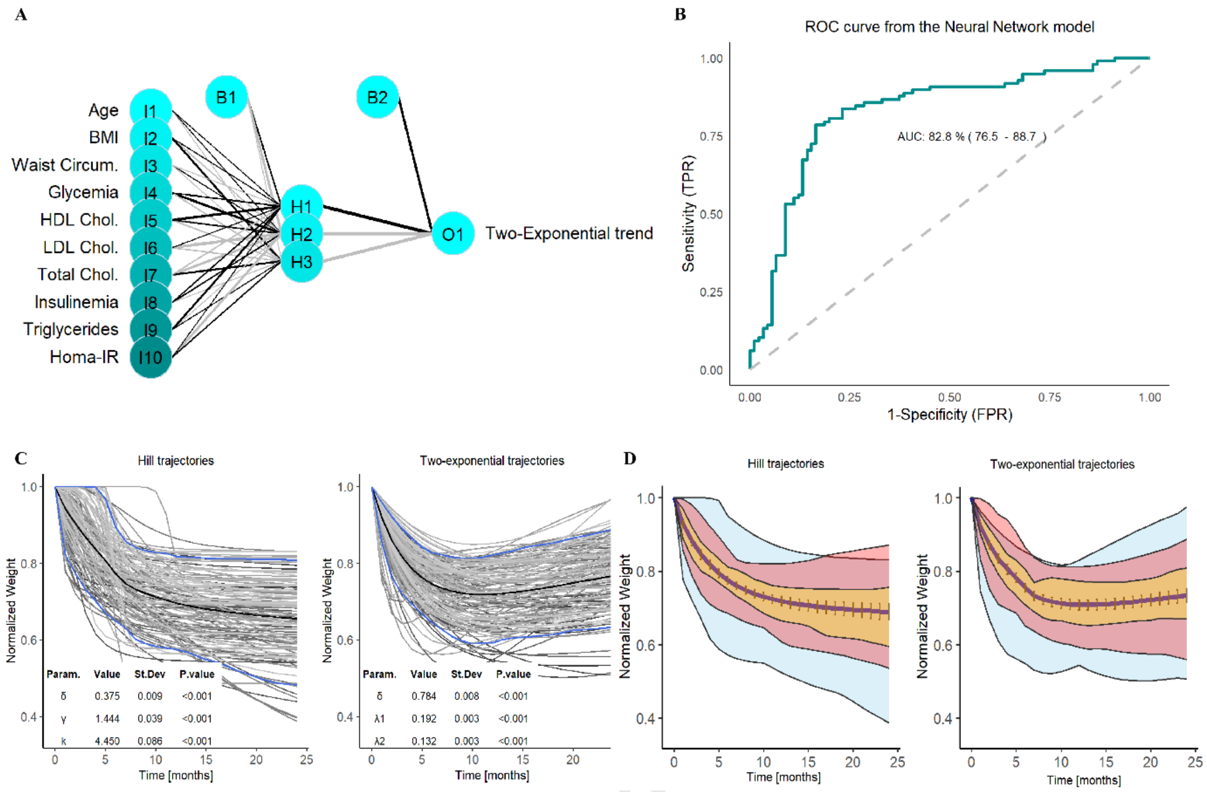
Treatment	33rd percentile	50th percentile	67th percentile
ALL	24.24	28.44	33.02
SG	18.29	25.62	31.03
RYGB	26.33	29.95	34.76


A
B
C
D
E
1
2
3
dim 1 (25.9%)
dim 2 (18.7%)
dim 3 (15.4%)
dim 4 (12%)
dim1
dim2
dim3
Age
Gender
BMI
Waist Circum.
Diabetes status
Glycemia
LDL-Chol
Triglycerides
Total Chol.
Homa-IR
Cluster 2
Cluster 3
B1
B2
H1
H2
H3
O1
O2
O3
%Delta Weight≤18
18<%Delta Weight≤30
%Delta Weight>30
Training set
Sensitivity (TPR)
1-Specificity (FPR)
AUC %Delta Weight≤18: 83.9 % (78.2 - 89.6)
AUC 18<%Delta Weight≤30: 63 % (55.7 - 70.4)
AUC %Delta Weight>30: 81 % (74.9 - 87.1)


A
Moderate sustained weight loss
B
Substantial sustained weight loss
C
Moderate weight loss+final weight regain
Normalized Weight
Time [months]
Param. Value St.Dev P.value
δ 0.224 0.010 <0.001
γ 1.168 0.061 <0.001
k 4.304 0.216 <0.001
Param. Value St.Dev P.value
δ 0.466 0.013 <0.001
γ 1.024 0.036 <0.001
k 4.670 0.202 <0.001
Param. Value St.Dev P.value
δ 0.880 0.005 <0.001
λ1 0.246 0.008 <0.001
λ2 0.201 0.008 <0.001
D
Subject 289
E
Subject 218
F
Subject 295


A
Moderate sustained weight loss
B
Substantial sustained weight loss
C
Moderate weight loss+ final weight regain
Normalized Weight
Time [months]
1.0
0.8
0.6
0
5
10
15
20
25


A
Moderate sustained weight loss
B
Substantial sustained weight loss
C
Moderate Weight loss+final weight regain
D
Substantial weight loss+final weight regain
Param. Value St.Dev P.value
δ 0.292 0.008 <0.001
γ 1.417 0.069 <0.001
k 4.032 0.138 <0.001
Param. Value St.Dev P.value
δ 0.463 0.009 <0.001
γ 1.451 0.046 <0.001
k 4.659 0.110 <0.001
Param. Value St.Dev P.value
δ 0.859 0.007 <0.001
λ1 0.178 0.004 <0.001
λ2 0.121 0.004 <0.001
Param. Value St.Dev P.value
δ 0.726 0.008 <0.001
λ1 0.186 0.003 <0.001
λ2 0.117 0.004 <0.001
E
Subject 79
F
Subject 83
G
Subject 231
H
Subject 72
Normalized Weight
Time [months]


A
Age
BMI
Waist Circum.
Glycemia
HDL Chol.
LDL Chol.
Total Chol.
Insulinemia
Triglycerides
Homa-IR
I1
I2
I3
I4
I5
I6
I7
I8
I9
I10
B1
B2
H1
H2
H3
O1
Two-Exponential trend
B
ROC curve from the Neural Network model
AUC: 82.8 % (76.5 - 88.7)
Sensitivity (TPR)
1-Specificity (FPR)
C
Hill trajectories
Normalized Weight
Time [months]
Param. Value St.Dev P.value
δ 0.375 0.009 <0.001
γ 1.444 0.039 <0.001
k 4.450 0.086 <0.001
Two-exponential trajectories
Param. Value St.Dev P.value
δ 0.784 0.008 <0.001
λ1 0.192 0.003 <0.001
λ2 0.132 0.003 <0.001
D
Hill trajectories
Two-exponential trajectories
Normalized Weight
Time [months]

Highlights

- Bariatric surgery treats obesity and type 2 diabetes, but weight loss varies.
- RYGB outperforms SG for weight loss at both 12 and 24 months post-treatment.
- Baseline metabolic health predicts weight loss outcomes.
- RYGB is superior to SG, even for metabolic high-risk individuals.
- Results support a precision-medicine approach in selecting bariatric procedures.