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Patient profiling for success after weight loss surgery (GO Bypass study): An interdisciplinary study protocol



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ABSTRACT

Despite substantial research efforts, the mechanisms proposed to explain weight loss after gastric bypass (RYGB) and sleeve gastrectomy (SL) do not explain the large individual variation seen after these treatments. A complex set of factors are involved in the onset and development of obesity and these may also be relevant for the understanding of why success with treatments vary considerably between individuals. This calls for explanatory models that take into account not only biological determinants but also behavioral, affective and contextual factors. In this prospective study, we recruited 47 women and 8 men, aged 25–56 years old, with a BMI of $45.8 \pm 7.1 \text{ kg/m}^2$ from the waiting list for RYGB and SL at Køge hospital, Denmark. Pre-surgery and 1.5, 6 and 18 months after surgery we assessed various endpoints spanning multiple domains. Endpoints were selected on basis of previous studies and include: physiological measures: anthropometrics, vital signs, biochemical measures and appetite hormones, genetics, gut microbiota, appetite sensation, food and taste preferences, neural sensitivity, sensory perception and movement behaviors; psychological measures: general psychiatric symptom-load, depression, eating disorders, ADHD, personality disorder, impulsivity, emotion regulation, attachment pattern, general self-efficacy, alexithymia, internalization of weight bias, addiction, quality of life and trauma;

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and sociological and anthropological measures: sociodemographic measures, eating behavior, weight control practices and psycho-social factors.

Joining these many endpoints and methodologies from different scientific disciplines and creating a multi-dimensional predictive model has not previously been attempted. Data on the primary endpoint are expected to be published in 2018.

Trial registration: Clinicaltrials.gov ID NCT02070081.

1. Introduction

Obesity is a world-wide major public health problem and to achieve sustained weight loss in obese individuals has proven to be a major challenge [1]. For adults with severe obesity surgery and notably Roux-en-Y gastric bypass surgery (RYGB) has consistently been shown to produce superior sustained weight loss and health benefits compared to all other non-surgical weight loss strategies [2–4]. Recent studies have shown comparable results following sleeve gastrectomy (SL) [5,6]. The surgery is clearly effective at the group level, but 30–40% of patients show inadequate weight loss at follow up [7,8]. This may cause medical, sociocultural and psycho-social problems for patients who are less successful in losing weight after either RYGB or SL and for society, it raises economic and ethical problems. Despite substantial research efforts, the mechanisms proposed to explain weight loss do not explain the large individual variation. According to previous studies, weight

loss after RYGB is not associated with malabsorption [9] or alterations in energy expenditure [10], but with reduced energy intake apparently resulting from changes in appetite [11]. These changes have been ascribed to alterations in the release of appetite-regulating gut hormones [10,12,13]. Moreover, evidence suggests that RYGB and SL may alter food preferences, potentially by altering the hedonic value of foods [14–16]. How the surgical intervention affects physical activity and how this may affect long-term outcomes has only been sparsely studied. Furthermore, socio-cultural and psycho-social factors have been shown to affect dietary intake, eating behavior and physical activity patterns [17–21]. These factors are therefore likely to also predict the patients' outcome of surgery. In addition, differential genetic background [22], as well as the intestinal microbiota [23], may contribute. Together, all these factors are potentially influencing weight loss after RYGB or SL. So far no single factor explains the variation in weight loss after surgery and therefore an interdisciplinary approach that addresses the multi-

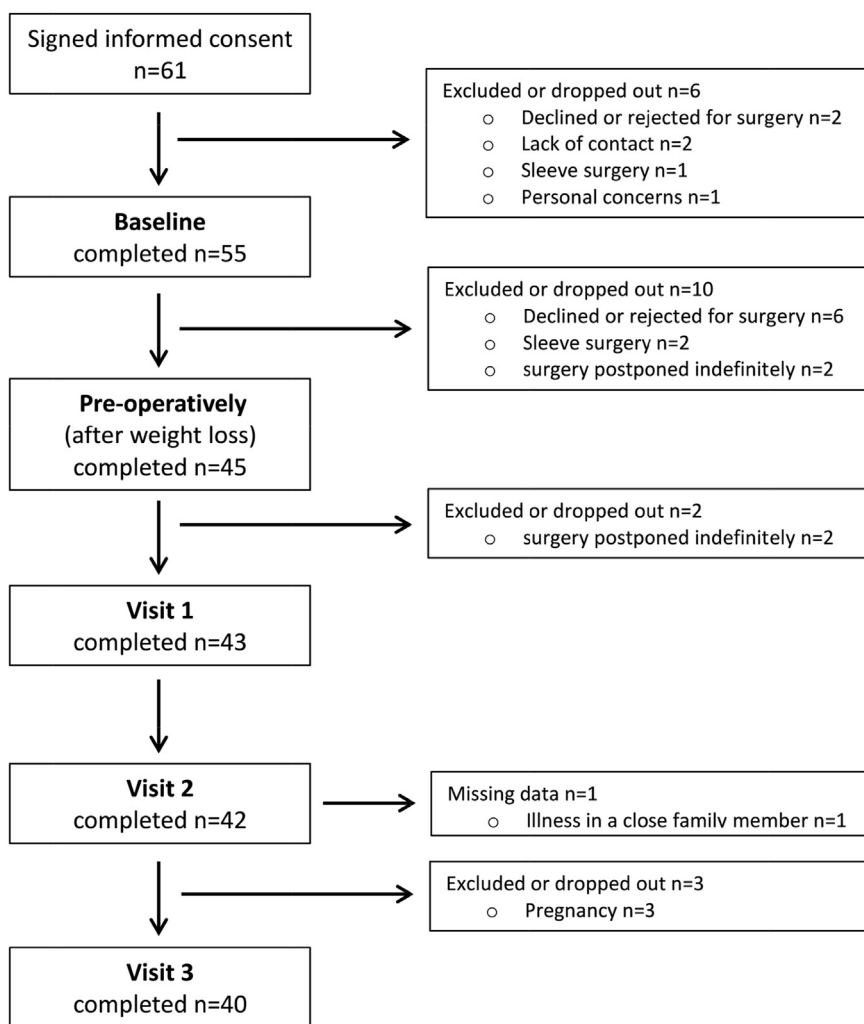


Fig. 1. Flow chart of recruitment. In the recruitment period, 143 patients were referred to surgery at Bariatric Clinic at Køge Hospital. Of these, 102 patients accepted to be contacted. Fifteen patients did not meet the inclusion criteria leaving a population of 87 potential participants of which 61 accepted participation. Forty participants have completed the final visit.

factorial nature of the problem, and take into account the interplay between physiological, genetic and psycho-social factors is needed.

The aim of this prospective study is to identify the multiple factors that determine weight loss after RYGB and sleeve gastrectomy. Adopting a novel interdisciplinary approach, we seek to clarify how the combination of multiple factors and their interaction account for the large individual differences in weight loss seen after RYGB and sleeve surgery. A second aim is to explore the possibility of identifying pre- and early post-operative factors associated with a poor weight loss and weight regain. Such factors could be targeted in order to prevent poor outcomes and potentially offer alternative interventions.

In the course of previous studies, our research team has experienced that a collaborative approach going beyond single discipline investigations is effective in enhancing our understanding of the complexity of weight loss after surgery [24]. With the current project, we aim to develop and deepen this experience in a comprehensive methodological design.

2. Methods

2.1. Participants

Participants included in this prospective study included all patients referred to RYGB or Sleeve gastrectomy at Bariatric Clinic, Køge Hospital, Denmark who accepted to participate and fulfilled the inclusion criteria. Indications for bariatric surgery in Denmark include age ≥ 25 y and BMI ≥ 50 kg/m² or BMI ≥ 35 kg/m² with comorbidities. Exclusion criteria include pregnancy as well as inability, physically or mentally, to comply with the procedures required by the study protocol. Furthermore, a weight loss of $\geq 8\%$ of initial body weight is required in Denmark as part of the preparation for surgery. Exclusion criteria related to the functional MR study/scans were: previous or current neurological diseases, pacemaker or other implanted electronic devices, a body weight or size that prohibited to lie in the scanner, or severe claustrophobia. Written informed consent was obtained from all of the participants.

2.2. Recruitment strategy

Participants were recruited from Bariatric Clinic at Køge Hospital, Denmark. Protocol details were explained and a baseline visit was scheduled for eligible participants. Written informed consent was obtained before any study-related activities were initiated. Participants were enrolled consecutively in the study from March 2014 to July 2015.

Initially, only participants referred to RYGB surgery were enrolled in the study and participants who chose to be treated with sleeve gastrectomy (SL) were excluded from the study (Fig. 1). However, as SL became increasingly popular in Scandinavia during the recruitment period, we decided to also include participants planned to be treated with SL from March 2015. We also decided to abandon the initial inclusion criteria of basal insulin ≥ 17 mIU/L, as participants with fasting insulin below this level turned out to make up a larger percentage than expected, and omitting these participants would decrease generalizability of the proband sample. These changes were deemed the most prudent if an adequate sample size should be reached within the

recruitment period. Notably as the referral criteria for surgery were governmentally altered during the recruitment period which made patient referrals decrease radically.

2.3. Outcomes

The primary outcome of this study was weight loss and sample size calculation was based on weight loss 18 months postoperatively. Secondary outcomes included improvements in metabolic health, here defined as the metabolic syndrome, and quality of life.

2.4. Study protocol

Patients were enrolled consecutively in the study from March 2014 to July 2015. The study included three visits preoperatively: A baseline visit, a psychological assessment interview visit (test day C) and a visit two weeks before surgery (pre-operative visit). Following RYGB or SL, visits were scheduled at 1.5, 6 and 18 months postoperatively (visit 1, 2, 3). Each visit included two to three experimental days (Test day A, B and D) in addition to measures of physical activity in free-living conditions, collection of feces and completion of questionnaires (Fig. 2 and Table 1). The study was performed according to the declaration of Helsinki and the protocol has been approved by the Scientific Ethic Committees of the Capital Region of Denmark journal no H-3-2013-138. The trial was reported to the Danish Data Protection Agency, journal no 2013-54-0522 and likewise registered in the database Clinical Trials at www.clinicaltrials.gov (ID NCT02070081). Last patient last visit was completed in April 2017.

2.5. Baseline

Baseline visit took place before the participants had started their 8% pre-operative weight loss (required according to Danish guidelines) and included two test days, A and B. Test day A included two questionnaires, a semi-structured qualitative interview performed in the homes of participants or in similar familiar setting of the participants' own choice, e.g. their place of work, a friends or parents' home. Test day B included multiple physiological measurements and took place at Department of Nutrition, Exercise and Sports, University of Copenhagen. Test day C, scheduled after baseline but before the operation, was a psychological assessment interview completed at the Bariatric Clinic at Køge Hospital, Denmark.

2.6. Pre-operatively

After the 8% weight loss was obtained and approximately one to two weeks before surgery the final preoperative visit was scheduled. Since the pace of weight loss differs between patients, the time from baseline to this visit differed. The visit included Test day A, B and D. Test day D took place at Danish Research Centre for Magnetic Resonance at Hvidovre Hospital, where neural sensitivity and the reinforcing value of food was assessed in a subsample of participants (all recruited from February 2015 to July 2015).

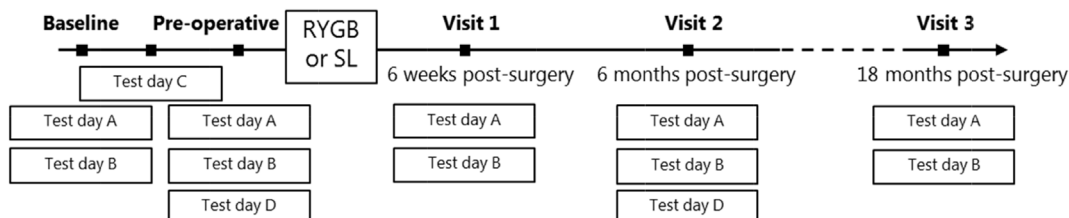


Fig. 2. Overview of test days and study design.

Table 1
Overview of study procedures and measurements.

Outcome	Baseline	Pre-operative	Visit 1	Visit 2	Visit 3
Test day A: Sociological and psychological assessment					
Questionnaires (sociodemographic measures and contextual factors)	x				
Baseline interview (weight biographies, expectations and incentive for seeking surgery, everyday life setting and schedules)	x				
Questionnaires (psychopathology and other psychological topics)	x			x	x
Follow-up interview (weight management, preferences and meal pattern, feeling of hunger and satiety, emotionally related eating, physical activity routines, bodily changes and awareness, dumping)		x	x	x	x
Test day B: Physiological assessment					
Anthropometry	x	x	x	x	x
Biochemical measures (metabolic profile, appetite hormones)	x	x		x	x
Appetite sensation and nausea (visual-analog scales)	x	x	x	x	x
Eating behavior (buffet meal test (buf.), picture display test (pic.))	Buf., pic.	Pic.	Pic.	Buf., pic	Buf., pic
Gut microbiota (feces sample)		x		x	
Stress level (cortisol)	x (sub-sample)				x
Taste preferences and perception	x	x	x	x	x
Vital signs	x	x	x	x	x
Genetic profile	x				
Physical activity, sedentary behavior, sleep (accelerometer)	x (6 days)	x (6 days)		x (6 days)	x (6 days)
Test day C: Psychological assessment					
Interview (psychological assessment interview, eating disorder assessment and personality disorder screening)	x				
Test day D: neural responsivity and reward					
Neural responsivity (fMRI)		x (sub-sample)		x (sub-sample)	
Rewarding value of food (Clicker test)		x (sub-sample)		x (sub-sample)	

2.7. Visit 1–3 (postoperatively)

The postoperative visits were carried out 1.5, 6 and 18 months after surgery. Here we followed up on all measures assessed preoperatively.

2.8. Surgical procedures

RYGB and SL were performed laparoscopically with the patient in a 10–20-degree anti-Trendelenburg position using 5 trocars. Operating time was normally about 45–60 min. In gastric sleeve resection, a vertical resection of the greater curvature was performed to reduce the size of the stomach to 80–100 ml. First, the omentum along the greater curvature was divided with an ultrasonic scalpel. Then a 34 FR calibration tube was introduced in the stomach, guiding the transection from 4 cm above the pylorus up to the angle of Hiss with staples. The resected part of the stomach was extracted through one of the trocar sites.

In Roux-en-Y gastric bypass, dividing the stomach with stapling instruments created a small gastric pouch of 30 ml. Sixty cm from the ligament of Treitz the jejunum was divided and the distal part of the small bowel was then anastomized to the pouch by placing the alimentary limb antecolic and antegastric. The gastro-entero-anastomosis was created with a linear stapler and closed by a running absorbable suture. The oral part of the transected jejunum was anastomized to the alimentary limb at 120 cm distal to the pouch. This left an alimentary limb of 120 cm, a biliary limb of 60 cm and a common limb of the rest of the small bowel. All patients followed a standardized fast-track program and were typically discharged on the first postoperative day.

3. Measures

In order to identify factors determining the variation in weight loss 18 months postoperatively, the study includes multiple physiological, psychological, and sociological measures described in more details below. The methodological design was informed by previous findings [10,13,25,26] within the research team.

3.1. Physiological and behavioral measures

3.1.1. Anthropometry

Body weight, height, hip and waist circumference were measured in the morning after an overnight fasting. Half-body scans were made by DXA to determine body composition.

3.1.2. Vital signs

Blood pressure and pulse were measured prior to a 400 kcal meal challenge and 15, 30, 60, 90, 120 and 180 min post-prandially.

3.2. Biochemical measures

Blood samples were drawn prior to a 400 kcal meal and 15, 30, 60, 90, 120 and 180 min post-prandially, at the baseline visit, visit 2 and visit 3. An additional blood sample was drawn after the buffet meals.

Blood samples were drawn into different tubes (fluoride tubes for glucose; chilled dry tubes for insulin, c-peptide, FGF-19, FGF-21 and bile acids; chilled EDTA tubes for total GLP-1 (with DPP-IV as inhibitor), PYY, total ghrelin, CCK and leptin). Samples in dry tubes were left to coagulate for 30 min before centrifugation, whereas the remaining samples were immediately cooled on ice and centrifuged at 4 °C. All blood samples were frozen at –80 °C until analyzed. Hair samples were collected in a subsample of participants at baseline and on all participants 18 months post operatively. Approximately 100 strands of hair were cut off as close to the scalp as possible. Samples were stored in envelopes until analyzed (as described elsewhere [27]).

3.3. Genetics

DNA was extracted from buffycoats at LGC Genomics (LGC, Middlesex, United Kingdom). All participants will be genotyped with the Illumina Infinium Human CoreExome BeadChip (CoreExomeChip) using Illumina's HiScan system at the Novo Nordisk Foundation Centre for Basic Metabolic Research's laboratory, Copenhagen, Denmark. The standard pipeline in Illumina Genome Studio software will be used for the genotype calling. Various weighted, normalized Genetic Risk Score (GRS) based on GWAS identified common variants known to associate

with for example BMI will be analysed for their impact on weight loss and related phenotypes.

3.4. Gut microbiome

Microbial DNA was extracted and will be subjected to amplification by polymerase chain-reaction, 16S rDNA sequencing using an Illumina MiSeq platform at the Novo Nordisk Foundation Centre for Basic Metabolic Research's laboratory. Microbial gene analyses, including taxonomic annotation and imputed functional characterization will be performed. An aliquot of feces from each visit will be stored in a research biobank for subsequent analysis of fecal biomarkers, and metabolites.

3.5. Appetite sensations

To evaluate subjective appetite sensations visual-analog scales were filled out prior to a 400 kcal meal and 15, 30, 60, 90, 120 and 180 min post-prandially at the baseline visit, visit 2 and visit 3. Ratings were marked on a 100-mm scale with the extreme limits of hunger, satiety, fullness, prospective food intake, nausea and desire to eat something sweet or fat respectively at each end.

3.6. Food preferences

Food preferences were assessed using an *ad libitum* buffet meal. The buffet meal was served at the end of the test day (4.30 p.m.) and energy intake prior to the meal was standardized between subjects and visits. The participants were instructed to eat according to their preferences and for as long as they want. They ate unmonitored and unaccompanied, in order to diminish social desirability bias. Twenty food items were served at the buffet meal: pork rib roast, chicken, fish cakes, nuggets, omelet, French fries, creamy potato gratin, bread, ketchup, remoulade, mayonnaise, skyr (yoghurt) with berries, vegetables, cut fruits, vanilla ice cream, chocolate sauce, cocoa meringues, biscuit cones with chocolate, sweet liquorice and Danish pastries. These food items varied along two dimensions - fat (high or low) and taste (sweet or savory) and they could be combined into culturally meaningful meals. It was thereby possible to organize these 20 food items into separate categories (high-fat, low-fat, savory and sweet) and four combined food categories (high-fat savory, low-fat savory, high-fat sweet and low-fat sweet) [28]. Total energy intake and intake from each of the food categories were registered. A blood sample was drawn after the meal. Participants were informed that the aim of the buffet meal test was to investigate how *ad libitum* intake affects different hormones while the real aim was to investigate how much was consumed from the different food categories.

Wanting was assessed by a picture display test where standardized pictures of the following 20 food items were shown: pork rib roast, French fries, nuggets, salty crackers, cheese, smoked fillet (cold cuts), omelet, carrots, crispbread, turkey strips, Danish pastries, vanilla ice cream, milk chocolate, pound cake, cookies, cut fruits, skyr (yoghurt) with berries, sweet liquorice, cocoa meringues and wine gum. As with the buffet meal, these 20 food items could be organized into combined and separate food categories. Pictures were displayed in a randomized order and the participants were instructed to choose the three food items they prefer the most in a prioritized order.

3.7. Neural sensitivity

The overarching aim of the functional MRI experiment was to assay the reward responsivity of mesolimbic structures to food images as a function of hormonal responses and the effects of RYGB and SL on these responses in the post prandial state. Specifically, we aim to elucidate the relationship between appetitive hormone trajectories, their effect on appetitive mechanisms of the mesolimbic and mesocortical

dopaminergic systems and the role of RYGB and SL on this suppression. We hypothesize that the appetitive effect of energy density in food cues will be suppressed post-surgery in the meso-limbic and mesocortical dopaminergic systems and that individual differences in the responses will be predictive of post-surgery weight trajectories. A minimal meaningful effect will be operationalized as a coefficient of multiple determination (R^2) larger than 10% in a multiple linear regression analysis encompassing neural, hormonal and nuisance covariates. Specifically this would mean the neural data from the hypothesized regions of interest would uniquely explain at least 10% of the variance in post-surgery weight trajectories, when accounting for all other relevant explanatory variables.

Participants underwent 3 structural MR scans: T1, T2, Flair-3D. The functional MRI scanning sequence consisted of an EPI, 3 mm isotropic, with a TR of 2.49s, a TE 30 min, 42 slices with 3 mm thickness, a FoV of 192, and a FoV of phase 100. Preparation time for the participants from arrival to in-scan was approximately 5 min. Scans were timed such that the fMRI sequence begins 30 min after the protein shake was served. This timing was designed to coincide with the expected peak in GLP-1 and PYY. fMRI scans took 12 min per session with 2 sessions per participant. All scans combined this result in a total scan time of approximately 45 min.

On the day of scanning (test day D) participants followed exactly the same food intake and timing as test day B. We engaged participants in a simple image repetition task (1-back working memory task) on standardized images of foods and objects, where food was either low or high calorie. We used an image bank for which the exact calorie content is known for each image. The design was a longitudinal 2×1 cohort study with 18-month follow-up. Covariates will be derived from gut hormonal trajectories (integrals, peak-trough magnitudes), progressive ratio task (see below), and *ad libitum* meal consumption. Planned comparisons include 1. The main effect of energy density pre vs. post-surgery, 2. Parametric effects of endocrine trajectory metrics on main effect of energy density and 3. Parametric effects of longitudinal changes in behavior and weight loss indices on the main effect of energy density.

3.8. Reward value of food

The reward value of a chocolate candy (M&M's) was assessed using a progressive ratio task to assess appetitive behavior shortly after the fMRI was completed. This test has previously been used in gastric bypass operated participants [14]. The participants were placed in front of a computer screen and 20 M&M's and instructed to click on a computer mouse to receive an M&M. The number of clicks needed to receive a reward increased progressively. When the participant stopped clicking (i.e. the "breakpoint" was reached and the effort exceeded the rewarding value of the chocolate candy) the number of clicks was registered. The progressive ratio task was carried out in the fed state (75 min after initiation of a 400 kcal meal). Visual-analogue scale to assess appetite was filled out before and after the progressive ratio task.

3.9. Taste preferences and taste perception

Participants were instructed in handling the samples and performing the sensory test in a room for sensory training. All sensory tests were carried out in individual booths in a sensory laboratory designed according to international sensory standards (ISO/ASTM). On each test day, participants were made familiar with the concepts and sensory properties of the five basic tastes by tasting aqueous solutions with supra threshold levels of the respective tastants. The participants were also familiarized with the sip-and-spit tasting procedure and response form used in the threshold measurements. Following the training, the participants participated in a sensory threshold test and a series of preference tests. During the session, participants were instructed to consume water (200 ml) and crackers (5 g) to rinse their palate and to

Table 2
Psychological questionnaire measures.

Theme	Assessment measure	Dimensions
General psychiatric symptom-load	SCL-90r	All items
Depression	BDI-II	All items
	PHQ	9 items regarding depression (PHQ-D)
Eating disorders	SCID-I	Module H
	EDE	8 items (EDE-Q8)
	EDI-3	3 subscales: BN, DT & BD (EDRC)
Adult attention-deficit/hyperactivity disorder	ASRS	6 items (ASRS-6)
Personality disorder	SAPAS	All items
Impulsivity	BIS-11	All items
Emotion regulation	DERS	All items
Attachment	ECR-R	All items
General self-efficacy	GSES	All items
Alexithymia	TAS20	All items
Internalization of weight bias	WBIS	All items
Addiction	YFAS	8 items
	AUDIT	3 items (AUDIT-C)
Quality of Life	IWQoL	All items
Post-Traumatic Stress	SSS-PSD	All items

Abbreviations: SCL-90r: Hopkins Symptom Checklist 90 revised. BDI-II: Becks Depression Inventory II. PHQ: Patient Health Questionnaire. SCID-I: Structured Clinical Interview for DSM disorders. EDE: Eating Disorder Examination-Questionnaire. EDI-3: Eating Disorder Inventory-3. ASRS: Adult ADHD Self-Report Scale. SAPAS: Standardised Assessment of Personality – Abbreviated Scale. BIS-11: Barret Impulsiveness Scale version 11. DERS: Difficulties in emotion regulation scale. ECR-R: Experiences in Close Relationships –Revised. GSES: General Self-Efficacy Scale. TAS20: Toronto Alexithymia Scale 20. WBIS: Weight Bias Internalization Scale. YFAS: Yale Food Addiction Scale. AUDIT: Alcohol Use Disorders Test. IWQoL: Impact of Weight on Quality of Life. SSS-PSD: Short Screening Scale for DSM-IV Posttraumatic Stress Disorder.

conform to the overall experimental protocol.

Threshold test: The taste threshold procedure was carried out according to ISO 3972, which was based on the ascending method of limits. The taste sensitivity was tested for sweetness (sucrose), however, to avoid an expectation effect over the repeated sessions another threshold test on a different basic taste was included (control). Thus the participants performed two threshold tests on each test day.

Preference tests: Preferences for different products illustrating sweet taste (apple juice), savoury flavour (tomato soup) and fat perception (chocolate drink) were registered. Samples were presented with a 3-digit code and tasted in a sip-and-spit approach. In each session all three sample types were tested in this order: soup, chocolate drink, and apple juice. Each preference session started with a warming up sample illustrating the respective product for which preferences were measured. Within the different tastes, the five sample variations were presented randomly to the participants. Preference measures were recorded using a 9 point hedonic scale [29], translated into Danish.

The taste stimuli were sucrose (99.5%, Sigma-Aldrich, USA), L-glutamic acid monosodium salt monohydrate ($\geq 98\%$, Sigma-Aldrich, France), caffeine (FCC, Sigma-Aldrich, China) and citric acid monohydrate (PA, Merck, Germany). Taste samples were prepared in neutral, tasteless tap water (TDS: 780 mg/L; hardness 22–30 dH). For the preference tests, three different products were prepared, an apple juice (10 °C), a tomato soup (65 °C) and a chocolate drink (10 °C). The apple juice (Organic, Rynkeby A/S, Denmark) was prepared in five variations with different levels of added sucrose (0; 5; 10; 15 and 20 g/L). The tomato soup (Karoline's køkken, Arla, Denmark) was prepared as a base soup (with no addition) and in four variations of either added monosodium glutamate (4; 8 g/L) or added sucrose (12 and 24 g/L). Chocolate drinks with different fat levels were prepared by adding 50 g/L Nesquik containing 78% sugar, 3.1% total lipids and 20.4%

cacao powder (Nestlé, Switzerland) to respectively fresh milk (0.4%, 1.5%; 3.0% fat; Arla, Denmark), neutral dairy coffee cream (10.0% fat; Arla, Denmark) and fresh whipping cream (38% fat; Arla, Denmark).

3.10. Movement behaviors

A 3-axis accelerometer (ActiGraph GT3X+) was used to assess physical activity and sleep. The participants were instructed to wear the ActiGraph in an elastic belt at the right hip for six days and seven nights and to remove it only during water activities. A sleep diary with information on sleep-onset and wake-up time was filled out during this period.

3.11. Psychological investigation

The relationships between obesity, psychopathology and other psychological variables have been investigated in several studies with mixed results [30]. The inconsistent findings point to different effects of being obese across individuals and to different pathways to obesity [31]. Another problem concerns the direction of causality. Many of the existing studies are cross-sectional and do not allow conclusions of whether the specific psychological problem is a consequence of obesity or is part of the etiology and thereby a cause for obesity. In this study, we covered a broad range of different psychological areas and functions. Most of these, e.g. depression [32], impulsivity [33], ADHD [34] and personality disorder [35] have in earlier studies been related to obesity and to patients seeking surgery for obesity. For other areas, we hypothesized a relationship based on research in eating disorders, e.g., emotion regulation, attachment and alexithymia [36,37], and yet other measures have been chosen in order to comply with the protocol of the Longitudinal Psychosocial Registry for Bariatric Surgery (PRAC), which is a German research initiative [38] we collaborated with.

The psychological investigation consisted of both quantitative and qualitative methods, in the form of psychometric self-report questionnaires and semi-structured interviews. All interviews were performed pre-operatively by one of two trained clinical research psychologists at the hospital clinic. All questionnaires were completed 3 times: At baseline, 6 months post-operatively (visit 2) and 18 months post-operatively (visit 3).

The following measures were applied (Table 2):

3.12. General psychiatric symptom-load

For a general description of the psychological habitus, the psychometric questionnaire “Hopkins Symptom Checklist 90 revised” (SCL-90r) was applied. The SCL-90r consists of 90 items to be answered on a scale from 0 to 4, and is a well-validated and widely used measure, with good to excellent internal consistency [39].

3.13. Depression

Depression was primarily measured with Becks Depression Inventory II (BDI), which is a widely used scale for measuring the severity of depression. The BDI-II consists of 21 items, featuring the symptoms of depression implemented in the diagnostic criteria in the DSM manual. The BDI-II is well validated and shows high internal consistency [40]. In coordination with PRAC, depression was also measured with the Patient Health Questionnaire (PHQ-D) [41].

3.14. Eating disorders

Eating disorder status, current and past was primarily assessed with the Structured Clinical Interview for DSM V (SCID-I), module H. The SCID-I is a widely used instrument for diagnostic assessment for all major mental diseases [42]. The applied version is updated with the latest changes in the diagnostic criteria for eating disorders as

represented in DSM-5, which besides Anorexia (AN) and Bulimia Nervosa (BN) also includes Binge-Eating Disorder (BED) [43]. Eating disorder psychopathology was also measured with the following questionnaires: The short version of the Eating Disorder Examination-Questionnaire (EDE-Q8) [44] and with three subscales from the EDI-3 [44].

3.15. Adult attention deficit hyperactivity disorder

We screened for adult attention deficit hyperactivity disorder (ADHD) with the Adult ADHD Self-Report Scale (ASRS), developed by World Health Organisation. The applied shortened version which consists of six items to be rated on a scale from 1 to 5, has shown good psychometric properties [45].

3.16. Personality disorder

We screened for non-specific personality disorder at the pre-operative interview, with the Standardised Assessment of Personality – Abbreviated Scale (SAPAS), which has been preliminary validated and shows promising psychometric properties [46].

3.17. Impulsivity

For the measurement of impulsivity, we used the Barret Impulsiveness Scale version 11 (BIS-11). The BIS-11 is a 30 item widely used self-report measure of impulsiveness, which has shown validity and good internal consistency [47,48].

3.18. Emotion regulation

In order to assess difficulties with emotion regulation, we used the “Difficulties in emotion regulation scale” (DERS) which has shown good internal consistency [49].

3.19. Attachment

Attachment refers to the different ways emotional bonds between individuals in close relationships manifest themselves. With the purpose of assessing patterns of adult attachment, we used the questionnaire “Experiences in Close Relationships -Revised” (ECR-R). The ECR-R explores 2 dimensions in the attachment framework; high to low avoidance and high to low anxiety. Within this matrix, scores can be used to classify respondents in the classical 4 adult attachment styles: Secure, preoccupied, dismissive and fearful [50]. The ECR-R has been validated and shown acceptable psychometric properties [51].

3.20. General self-efficacy

The General Self-Efficacy Scale (GSES) was used to assess global self-beliefs in one's competence to deal with stressful and challenging events. The scale has demonstrated good validity and adequate internal consistency [52].

3.21. Alexithymia

The term alexithymia covers the inability to describe and identify emotional states in the self. We measured this concept with the “Toronto Alexithymia Scale 20” (TAS20) which has been validated and shows adequate to good internal consistency [53].

3.22. Internalization of weight bias

The Weight Bias Internalization Scale (WBIS) [54] was used to assess internalized weight bias, i.e., an overweight or obese individual's degree of applying the public weight stigma to the own person. The

WBIS has evidenced validity and internal consistency [55].

3.23. Addiction

We assessed two aspects of addiction: *Food addiction* was investigated with a short version of the Yale Food Addiction Scale (YFAS) [56]. The items were selected based on an item analysis on PRAC data. The YFAS evidenced adequate validity and internal consistency [57].

Alcohol consumption was assessed with a shortened version of the Alcohol Use Disorders Test (AUDIT), developed by the World Health Organization. The AUDIT-C has adequate validity and internal consistency [58].

3.24. Quality of life

Quality of life specifically with regards to being overweight was assessed with the Impact of Weight on Quality of Life-Lite questionnaire (IWQoL-Lite), covering 5 domains: *Physical function, self-esteem, sexual life, public distress and work*. The IWQoL displays adequate validity and internal consistency [59].

3.25. Trauma

A short screening scale for post-traumatic stress disorder (SSS-PSD) [60] was used for assessment of posttraumatic symptoms. A diagnosis of posttraumatic stress disorder can be derived from the scale. The SSS-PSD has evidenced adequate validity [61].

3.26. Psychological assessment interview

A broad psychological assessment interview was performed prior to surgery at the hospital clinic. In order to create a more coherent picture of the participants' psychological resources and challenges topics already covered by the questionnaires were investigated with a qualitative approach, and sensitive topics, such as previous mental disease, suicide attempts, sexual abuse and bullying in childhood as well as participants' psychological understanding of their weight development and motives for pursuing surgery were explored. The interview was based upon previously published instructions for pre-bariatric psychological assessment interviews [62–67]. After each interview, a psychological case-report profile, based upon both questionnaires and the interview case-report was composed which summarized key components in the participants' resources and possible post-surgical challenges. It concluded with a classification of participants in 3 groups: High risk, some risk, low risk for failure, describing the participant's ability or possible inability to conduct a healthy, satisfactory and maintained weight loss, seen from a psychological perspective.

3.27. Sociological and anthropological measures

In order to map patterns of everyday behaviors, attitudes, and resources in relation to food and weight a comprehensive mixed methods data design was adopted. The sociological and anthropological investigation consisted of both quantitative and qualitative data, in the form of a self-report questionnaire and repeated semi-structured interviews.

The **GO Bypass questionnaire** included: Socio-demographic measures (age, gender, income level, education, marital or family status, and employment status), contextual factors (work and life pressures, work control, work load and working conditions, daily schedules, and social obligations) and psycho-social factors (self-evaluated general health status; stressful life-events, interpersonal problems, and social and emotional support).

The **semi-structured interviews** assessed the following themes:

3.28. Eating practices

Eating practices were operationalized in the following dimensions: Meal pattern, food-related knowledge and competences, emotionally related eating, and feeling of hunger and satiety. The repeated follow-up interviews identified changes over time.

3.29. Weight control

This theme included: Weight biographies, previous weight loss attempts, and previous physical activity. Further, weight management and current physical activity routines were re-assessed via the repeated follow-up interviews.

3.30. Psycho-social factors

Self-evaluated general health status, stressful life-events, interpersonal problems, and social and emotional support were assessed and re-assessed. Changes in these factors were evaluated through all the interviews during the entire study period.

The qualitative interviews included five consecutive interviews with each participant conducted by the same interviewer, who was a skilled anthropological researcher. The interviews were in-depth, open-ended conversations seeking comprehensive, detailed and concrete information about the broadest range of lived experience related to severe obesity and the processes related to going through surgery. This information-rich data [68] opens up for a more targeted analysis, which allows for a deeper and fuller understanding of factors which have been identified as important for sustained weight loss. These are: Social resources, and support [65,66], patients' body perceptions, and aspirations for and concerns about weight loss after surgery [69,70], patients' different eating strategies, i.e. how they perceive and handle eating behavior, meal timing and food choice post-surgery [67,68]. In-depth knowledge of how patients evaluated their body and monitored weight changes in their daily practices [69,70] made investigations of the causes of such practices possible and thus how they contributed to e.g. eating behavior and food choice post-surgery.

The qualitative interviews assembled comprehensive qualitative knowledge about topics already partly covered by psychological and physiological measures. This contextualized findings from both methodologies. Previous work from team members suggests that this will allow for more accurate analysis [22]. The aim was to identify new decisive factors and to investigate the continuous properties of phenomena which were assessed at discrete time points in the physiological measures, e.g. nausea, pain and dumping in relation to eating. In order to integrate data across disciplines, the qualitative data from interviews were quantified by way of an initial content analysis identifying factors decisive for weight development. Factors were then assigned a score (categorical, ordinal or continuous), rated on the basis of the strength of the factor in the individual interview.

4. Sample size calculation

The power calculation was based on unpublished follow-up data from a previous study (ClinicalTrials.gov ID NCT00939679) [10]. Here we found a mean difference of 16.4 ± 3.4 kg between good ($> 60\%$ excess weight loss) and poor responders ($< 60\%$ excess weight loss respectively) 18 month after surgery. Based on own data as well as data from the literature [71] we expected 23–25% of the recruited participants to be characterized as poor responders. With a 5% significance level and 80% statistical power, we estimated that a total of 50 participants needed to complete all five visits in order to detect a difference in body weight of 16.4 kg (SD 13.41 kg). We estimated a dropout rate of 10% from baseline to 18 months post-operative, and we therefore recruited until 55 participants had completed the baseline visit.

For the qualitative parts of the study, data saturation was secured at

$n = 12$ [72]. With a sample size of 55, an expected drop out of 10% and assuming that 23–25% of the completers will have $< 60\%$ excess weight loss at 18 months it was thus expected that 12 participants will be poor responders.

5. Statistical analysis

All outcomes will be analyzed using available-case analyses, which utilize data from all participants until drop-out or completion. Specifically, outcomes will be analyzed by means of linear mixed models including one or more of the above-mentioned measures in combination as well as subject-specific random effects and adjustment for baseline outcome, age, and gender and, possibly, other relevant confounders. Baseline characteristics presented are based on the study population at the time of the baseline measurements. Continuous variables are summarized as mean \pm SD whereas categorical outcomes are reported as n (%).

6. Results

Fifty-five participants (47 females and 8 males) were included in the study. The participants were 25–56 years old with a mean BMI of 45.8 ± 7.1 kg/m² at the time of inclusion. Twenty-four percent of the participants were diagnosed with type-2-diabetes (Table 3).

Sixty-one participants gave signed informed consent, however, five participants dropped out and one participant was excluded prior to the baseline visit. Fifty-five participants completed the baseline visit. Ten participants dropped out or were excluded prior to the pre-operative visit. The major reason for dropout was surgery rejection by the bariatric team at Køge Hospital (Fig. 1).

7. Discussion

Understanding the multiple factors and mechanisms involved in the development of obesity as well as in successful management of weight loss and weight loss maintenance among severely obese individuals calls for an interdisciplinary approach. Joining multiple scientific disciplines in all phases of this study, from developing the idea to analyzing the data, is therefore, a major strength of our study design. We have aimed at taking interdisciplinary research a step further by *a priori* designing a study with one shared goal; to explain the variation in weight loss after gastric bypass and sleeve gastrectomy by integrating multiple physiological, psychological, behavioral, sociological and

Table 3
Baseline characteristics.

	Participants (n = 55)
Gender, n (%)	
Female	47 (85)
Male	8 (15)
Age (years), mean \pm SD	39.6 \pm 9.6
Age (years), n (%)	
25–34.9	21 (38)
35–44.9	11 (20)
45–54.9	20 (36)
≥ 55	3 (5)
Weight (kg), mean \pm SD	132.5 \pm 24.8
BMI (kg/m ²), mean \pm SD	45.8 \pm 7.1
BMI (kg/m ²), n (%)	
< 40	12 (22)
40–49.9	29 (53)
50–59.9	12 (22)
≥ 60	2 (4)
Type 2 diabetes, n (%)	12 (24)
Surgery, n (%)	
Roux-en-Y gastric bypass	33 (77)
Sleeve Gastrectomy	10 (23)

anthropological data. All data were collected on the same participants at the same time points which increased homogeneity of data and decreased bias caused by interpersonal variability and viability caused by differences in time and setting. Moreover, as most themes addressed in the study, such as for instance food preferences, eating behavior, food avoidance/aversion, reward-based eating, and physical activity were investigated through several methods and in different settings we increased the possibility of detecting and explaining complex behavioral changes. Thereby we add nuance to concepts and themes and explanatory power to interplays and synergy effects between factors. Similar, interdisciplinary approaches have never been published before making the GO Bypass study genuinely novel.

In our design, we have included several novel methodologies, in particular in regards to eating behavior. Investigating eating behavior in humans is challenging and previous studies on food preferences rely mainly on verbal reports. In contrast, the buffet meal test included in the study targeted actual behavior and measured food selection in a context designed to mimic everyday practices. Measures of neural sensitivity in response to food stimuli, sensory perception and liking of different flavors, feeling of hunger and satiety, adverse experiences (nausea) when eating, appetite hormone responses and effects on other signaling molecules hypothesized to interfere with aspects of eating, questionnaires targeting eating disorders and personality traits together, and qualitative interviews focusing on emotional eating and meal patterns were also included to elucidate how gastric bypass and sleeve gastrectomy affects eating behavior. The combinations of these measures are examples of how we seek to unravel complex phenomena by joining data from different disciplines in the preplanned analytical models.

A potential weakness of our study design is the time-consuming demands we put on participants. This could have led to drop out. We sought to counteract this by building confidence and familiarity with participants through the consecutive personal interviews and other meetings. Further, we decided to change the inclusion criteria after start of recruitment and included all patients independent of state of glycemic control and surgical procedure. These changes disturbed the homogeneity of our study sample somewhat but we believe that the primary endpoint was better elucidated and generalizability was increased when the study population was more representative for the typical patients undergoing obesity surgery in Denmark.

Main results from GO Bypass will be published in 2018 when the joint analysis has been completed. Preliminary results have recently been published [16,73] and we will continue to publish 6-months data and data on secondary endpoints throughout the coming years. Some of the psychological data (PRAC) will furthermore be integrated in large cohort studies, PRAC [38,74].

Conflicts of interest

Julie Berg Schmidt, Bodil Just Christensen, and Louise Tækker reported receiving a research grant from University of Copenhagen. Lotte Holm receives honoraria as editor from Elsevier Publishers, Amsterdam, The Netherlands. Hartwig R. Siebner has received honoraria as senior editor from Elsevier Publishers (NeuroImage) and grant support from Biogen-Idec, Denmark. Jens Juul Holst reported being a partner of the EU project Full4Health, he serves as an advisory board member for Glaxo, Smith, Kline, Novo Nordisk, and Zealand Pharmaceuticals and receives grants from Novartis and Merck and consulting fees from Novo Nordisk. Anders Sjödin reported receiving a research grant from University of Copenhagen and the Lundbeck Foundation. The other authors declare no competing interests.

Authors' contributions

The study was initiated by JBS and BJC. The research idea and the study design was developed by JBS, BJC, MSN, LT, LH, SL, CLR, OH,

LN, AKF, and AMS. Collection of data and data analysis is carried out by JBS, BJC, MSN, LT, LH, SL, WB, CR, JJH, TH, AH, OH, TM, HS, LN, AKF, and AMS. All authors contributed to the writing of and approved the final manuscript.

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