Translational analyses of ingestive behaviour after gastric bypass (Ref: STL/5062/14)

SHORT REPORT

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EVIDENCE BRIEF

Why did we start?

Gastric bypass surgery (GBS) leads to significant and sustained weight loss and improved co-morbidities in individuals with severe obesity. While reduced energy intake (EI) is the primary driver of weight loss, the underlying mechanisms of the weight change trajectory are not well understood. In particular, the evidence base has been constrained by a lack of fit-for-purpose methodology in assessing food intake coupled with follow-up studies that are of relatively short duration.

What did we do?

We conducted a fully residential observational study using covert, objective methodology to evaluate changes in 24-hour food intake in patients (n=31) who underwent GBS at four time points (1 month pre-surgery and 3-, 12- and 24-months post-surgery), compared with weight-stable controls (n=32). The main study outcomes included change in EI, macronutrient intake, food preferences, and eating behaviours (speed, frequency, and duration of eating). Other physiological changes that may influence EI and weight regulation including changes in body composition, circulating appetite hormones, resting metabolic rate, total energy expenditure and gastrointestinal symptoms were also evaluated.

What answer did we get?

While there was a reduction in overall mean EI, the outcomes of this study did not support the initial hypothesis that this is associated with macronutrient specific changes in food intake. Rather, the reduction in EI was primarily facilitated by the consumption of smaller amounts of the same foods as consumed pre-surgery, consumed more frequently.

What should be done now?

This study was the first to objectively measure food intake across multiple eating occasions in patients after GBS. Understanding which mechanisms contribute to a reduction in EI and weight loss following surgery could potentially help identify those individuals who are most likely to benefit from GBS as well as those that may need more targeted intervention to optimise their weight loss post-surgery. Furthermore, clarification of these mechanisms may also inform targeted approaches for non-surgical treatments of obesity and type 2 diabetes.

This study protocol and the employment of robust fit-for -purpose experimental tools present a unique opportunity to gain a better understanding of the **long-term** dynamics of food intake, food preferences and weight trajectory by following up this well-characterised cohort at 5 years post-surgery.

Background

Gastric bypass surgery (GBS) is a safe, effective treatment for individuals with severe obesity (Colquitt *et al.* 2014) and leads to improvements in associated co-morbities including type 2 diabetes mellitus (T2DM) (Cummings *et al.* 2016) and cardiovascular disease (Chrotowska *et al.* 2013). The most frequently performed procedure is the Roux-en-Y Gastric Bypass (RYGB), and more recently the One-Anastomosis Gastric Bypass (OAGB) which are equally effective for both weight loss (Solouki *et al.* 2018), cardiovascular and quality-of-life outcomes, (Lee *et al.* 2005; Magouliotis *et al.* 2019).

The exact mechanism(s) underlying the profound weight loss and sustained weight maintenance remain elusive but involve a complex interaction between physiological, psychological, and behavioural factors. Although a decrease in energy intake (EI) is the main driver of weight loss (Warde-Karmar *et al.* 2004; Kruseman *et al.* 2010; Moize *et al.* 2013; Janmohammadi *et al.* 2019) this cannot be fully explained by purely restrictive and malabsorptive mechanisms (Abdeen and le Roux, 2016; Mahawar and Sharples, 2017). Other proposed mechanisms include changes in hunger and satiety (Morinigo et al., 2006; le Roux et al., 2007) caused by changes in circulating gut hormones (Falkén *et al.* 2011; Holst *et al.* 2018), changes in eating patterns such as reduced portion sizes without compensatory increases in meal frequency or duration (Zheng *et al.* 2009; Laurenius *et al.* 2012), shifts in dietary energy density (ED) (Laurenius *et al.* 2013) resulting from changes in food selection and/or changes in food preferences (Kenler *et al.*1990; Nielsen *et al.* 2019). Selective changes in macronutrient intakes and the associated impact on EI is a particularly contentious issue. Evidence from animal studies suggest that there is a postoperative decrease in fat and sugar intakes (le Roux *et al.* 2011; Mathes *et al.* 2015; Mathes *et al.* 2016; Hyde *et al.* 2020). However, the evidence from human studies regarding changes in relative macronutrient intake in the short-term is equivocal (Mathes and Spector, 2012), with studies variously reporting a decrease (Kenler *et al*., 1990; Olbers *et al*., 2006; le Roux *et al*., 2011) or no change (Brolin *et al*., 1994; Laurenius *et al*., 2012) in the intake of high fat/high sugar foods.

The elucidation of the underlying mechanisms of postoperative weight loss has been severely hampered by inconsistencies in bariatric research methodology and further compounded by differences in the analysis, interpretation and presentation of results (Coulman *et al*., 2013; Hopkins *et al*., 2015; Mocanu *et al*., 2019). In particular, there has been overwhelming reliance on and acceptance of the purported validity of subjectively reported food intake and food preference data without proper acknowledgement that biased food intake data are a fundamental obstacle in understanding the dynamics of food selection and intake following

GBS (Redpath *et al.,* 2021). To date, only one research group has objectively observed food intake behaviour in a bariatric surgery population (Nielsen *et al.,* 2017; Nielsen *et al*., 2018). The observed reduction in EI was non macronutrient specific and was accounted for by consumption of smaller portion sizes of the same foods that were consumed pre surgery. However, these potentially significant and independently validated findings are confined to one eating event which limits their extrapolation.

The integrity of the existing evidence base is further constrained by the frequency and duration of study follow-up. Most of the current evidence regarding post-operative EI is based on short-term (up-to 12 months post-surgery) and/or single time point studies. However, this is the stage when patients are losing significant weight and it is inconceivable that these studies could capture the dynamics of food intake behaviour and the subsequent impact on the longer-term weight trajectory.

Consequently, this study was specifically designed to address the above limitations by employing fit-for-purpose methodology in a fully residential setting to help clarify the mechanisms underpinning the dynamics of food selection and intake at four times up to 2 years post-surgery.

Aims and Objectives

This project forms part of a collaborative study between Ulster University, University College Dublin, and Florida State University and was funded by the US-Ireland Research and Development grant. The overall study, entitled 'Translational Analyses of Ingestive Behaviour After Gastric Bypass' brought together different, but complementary, state-of- the art experimental approaches to evaluate if the observed reduction in food intake following GBS is linked to a change in palatability of foods and/or is a learned adjustment in feeding behaviour by using direct measures of target behaviors in humans that can also be applied to animal models and vice-versa. The translational approach included the application of animal models (Florida State University), complemented by acute clinical studies in humans, which isolated the role of the gut hormone response (University College Dublin), and a fully residential observational study (Ulster University).

Project specific study aim: To evaluate the nature of the transition in food intake in patients who have undergone GBS during a dynamic phase of weight loss using covert and objective tracking of food intake and eating behaviours assessed under fully residential conditions. In addition, associations with Resting Metabolic Rate (RMR), free-living total energy expenditure (TEE), and body composition were evaluated. It was hypothesised that the interplay between the various dimensions of dietary intake, eating behaviour, energy expenditure and gut hormone responses are key in driving the weight change trajectory following GBS.

Methods

Recruitment

Patients scheduled to undergo GBS (n=34) and weight-stable controls (n=32) were recruited (Figure 1). Patients were referred for either RYGB or OAGB at several hospitals/health trusts across the United Kingdom (UK) and Republic of Ireland (ROI). Patients recruited from England were referred for surgery (provided by the NHS) by their General Practitioner, those recruited in Northern Ireland were self-referred and having their treatment privately, and patients from ROI were recruited from a group clinically selected to undergo GBS as part of a pilot programme for the management of T2DM. For all participants, the exclusion criteria were: <18yrs of age, pregnancy/lactation, food allergies/dietary restrictions and/or gastrointestinal conditions or medications that may affect food intake.

Control participants were weight-stable (>6 months) individuals time-matched to the patient group and with no planned weight changes recruited using email, social media and word-of-mouth recruitment methods.

For all participants, the exclusion criteria were: <18years of age, pregnancy/lactation, food allergies/dietary restrictions and/or gastrointestinal conditions or medications that may affect food intake.

Study Protocol

At four time points (1 month pre-surgery, 3-, 12- and 24- months post-surgery) participants undertook a 36hr residential period, starting late afternoon on day 1 and ending at lunchtime on day 3, in the Human Intervention Studies Unit (HISU) within the Nutrition Innovation Centre for Food and Health (NICHE), Coleraine Campus, UU. The covert monitoring of 24h food intake, began on the morning of day two (~7am) until bedtime (11pm). Participants remained in the HISU for the duration of each study visit but with access to a range of sedentary activities including reading and crafts, with televisions in communal areas and bedrooms. An overview the residential visit protocol is provided in Table 1.

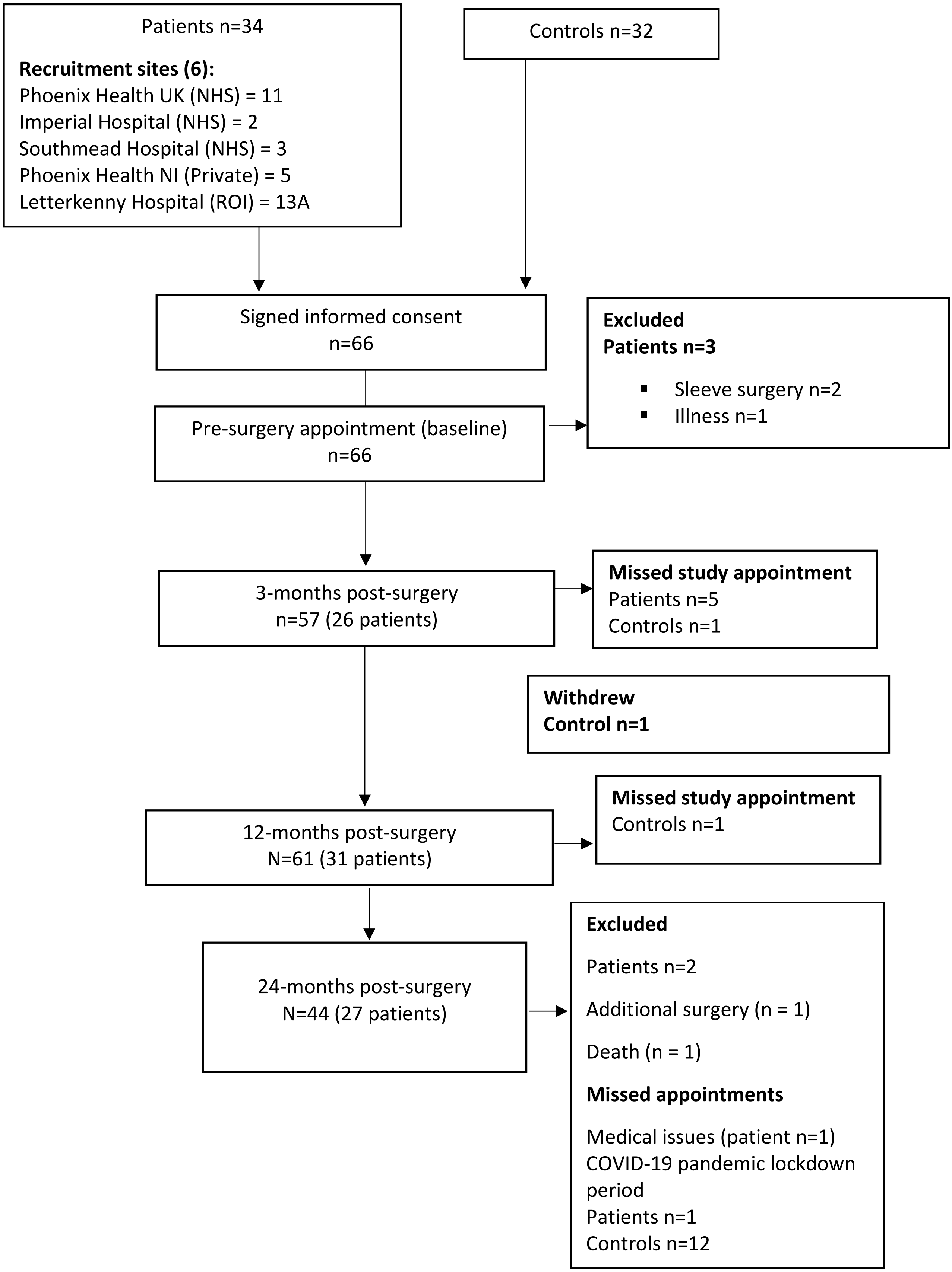


Figure 1: Overview of participant recruitment, progression, and retention. NHS National Health Service **ROI** Republic of Ireland

Table 1: An overview of the residential visit protocol$

Day 1	Day 2	Day 3
▪ Arrive late afternoon/evening ▪ Standardised dinner provided if requested ▪ Doubly labelled water (DLW) measurement of total energy expenditure. Baseline urine sample collected from subset of patients (n=7) ▪ Fast from 10pm	▪ Resting metabolic rate on waking (participant-defined wake up time; ~6am-8am) ▪ Buffet breakfast ▪ 24h ad-libitum access to food throughout measurement period ▪ Body composition measurements ▪ DLW administered to subset of patients (n=7) ▪ Medication use/ gastrointestinal symptoms Questionnaires* ▪ Qualitative discussion (final time-point only) ▪ Fast from 11pm	▪ Fasted (28ml) blood draw* ▪ 60 mins allocated to eat a standardised breakfast ▪ 90 min postprandial (8ml) blood draw* ▪ Leeds Food Preference Questionnaire ▪ 24h post-DLW urine sample collected from sub-set of patients (n=7) £^ ▪ End of visit (~1pm) ▪ 7d free living physical activity assessment using Actigraph monitors from sub-set of patients from Day 3-Day 10 (n=7)*£

$Protocol conducted at -1 month, 3 month, 12 month & 24 month post-surgery; *additional measures included; £under free living conditions; ^additional spot urine samples collected at Day 7 & Day 14.

Food provision

Prior to the baseline visit, all participants completed a food choice questionnaire consisting of 96 food items listed in random order and representative of 6 macronutrient (expressed as %energy) mix groups (high fat/low fat, high complex carbohydrate/low complex carbohydrate, high simple sugar/low simple sugar, high protein/low protein; Table 2). The purpose of the questionnaire was to identify a personalised menu based on the highest expressed hedonic response within each food group (9 foods from each of the 6 groups). The **same** personalised menu of 54 foods were then provided at each time point.

Table 2. Macronutrient paradigm for the foods presented to study participants

	High Simple Sugar	High Complex Carbohydrate	High Protein
High Fat	n=9 Fat >40% energy Sugar >30% energy e.g. chocolate muffin, twirl, ice cream	n=9 Fat >40% energy CCHO >30% energy e.g. croissant, steak pies, apple pies	n=9 Fat >40% energy Protein >13% energy e.g. peanuts, bacon, cheese
Low Fat	n=9 Fat <20% energy Sugar >30% energy e.g. banana, grapes,	n=9 Fat <20% energy CCHO >30% e.g. sesame bagel, white	n=9 Fat <20% energy Protein >13% energy e.g. ham, Quorn, fat-

	sugar-free meringues	bread, sugar-free jelly	free cottage cheese,

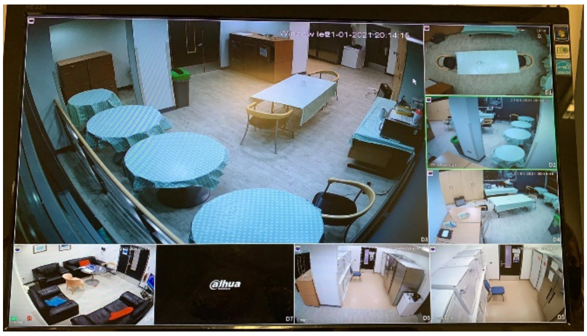
Foods were presented in different formats; hot and cold traditional 'breakfast' foods (n=6) were presented as a buffet, while lunch/snack foods (n=36) were available ad-libitum from each participant's assigned refrigerators and cupboard for storing non-perishable foods/beverages. Evening meals (n=12 dishes) were selected from individually tailored menus featuring hot savoury dishes (n=6) and desserts (n=6) with no restriction on the number of choices that could be made. Participants were advised to consume only the foods provided to them and not to share food items. Researchers were not present while participants were eating. Meal and snack times were not researcher prescribed in advance, rather participants could select to eat at time(s) of their choosing.

<u>Outcomes</u>

Dietary Intake:

Following an overnight fast from 10 pm (Day 1) the ad-libitum food intake of each participant was directly and covertly measured from approximately 7am to 11 pm (Day 2) by weighing all foods before serving together with leftovers. At the end of each visit, the bins in the participants' bedrooms were checked for empty food packages and any leftover foods or drinks that were taken from the participants fridge/cupboard. These food items were also weighed and recorded. The food intake at each time point was verified using the CCTV.

Dietary intake data were computer analysed using a database developed specifically for this study. Outcome measures were total EI (MJ/d), energy density (ED) (defined as kJ/g of food and energy-containing beverages consumed) and relative macronutrient (%EI) and macronutrient mix group (%EI) intake.



Food intake behaviour:

CCTV footage also enabled the measurement of a number of eating behaviours including:

- Eating frequency (n): A discrete eating occasion was defined as a continuous period of eating (where at least 210kJ(50kcals) was consumed) that was terminated with a pause of >5 minutes between eating episodes.

- Eating duration (min), size of eating occasions (g, kJ) and rate of eating (g/min, kJ/min)

- Timing of eating: eating occasions were subsequently divided into 4-hour eating periods (epochs); namely epoch 1: 7-11am, epoch 2: 11.01am-3pm, epoch 3: 3.01–7pm, epoch 4: 7.01-11pm.

Food Preferences:

Prior to leaving the HISU on day 3 and 2 hr after breakfast after all other dietary measurements had been completed, participants completed the Leeds Food Preference Questionnaire (LFPQ) (Finlayson et al. 2008). This questionnaire has been validated in different populations (Alkahtni et al., 2016; Oustric et al., 2020) and has been previously used to measure food preferences in individuals with obesity (Dalton et al., 2013; Blundell et al., 2017).

The LFPQ is a computer-based measure of both explicit and implicit components of food preference and is a validated measure of food 'liking' (hedonic pleasure) and food 'wanting' (desire to consume) of a range of common high-/low-fat, sweet/savoury food items.

Energy expenditure

1. **Total Energy Expenditure (TEE)**

TEE was measured under free-living conditions over 14 consecutive days by the doubly labelled water (DLW) method (Schoeller and van Santen, 1982; Westerterp, 2017) in a subgroup of patients (n=7). TEE is estimated by enriching the participant's body water with two stable isotopes: deuterium ($^{2}H_2$) and oxygen-18 (^{18}O) and determining the difference in elimination rate between both isotopes. The method is based on the principle that $^{2}H_2$ is eliminated as water, corresponding to water output, and ^{18}O exits the body as both water and expired CO_2 with the difference between the elimination rates providing a measure of CO_2 production from which the mean TEE over the measurement period is calculated using classical indirect calorimetric equations.

2. **Resting Metabolic Rate (RMR):**

RMR (the rate at which the body uses energy while at rest to maintain vital functions such as breathing and keeping warm) was measured (over 8 minutes) under standardised conditions on the morning of Day2 by an open-circuit portable indirect calorimeter (ECAL, Metabolic Health Solutions). Values were calculated as energy requirement per day (MJ/day) as well as on a per kg body composition basis (kJ/kg body weight, kJ/kg lean body mass, kJ/kg fat mass).

3. **Energy cost of Physical Activity**

The Physical Activity level (PAL) was calculated as: PAL= TEE/RMR.

Body Composition:

Body weight (kg) and body composition (Fat Mass (FM), Lean Body Mass (LM) and Visceral Adipose Tissue (VT)) were assessed under standardised conditions on Day 2 of each study visit using the total body GE Lunar iDXA scan (GE Healthcare, USA). A qualified and experienced radiographer verified all the scans.

Medical Information:

At each study time point researchers recorded participants' medical information including any pre-existing medical conditions and details of any medications and dietary supplements taken.

Qualitative Data

Semi-structured interviews were carried out at each participant's (n=31) final visit at 24 months post-surgery. The interview consisted of 10 subject domains to gain an insight into the complexity of patients' ingestive behaviours following GBS and the barriers and facilitators of weight loss. The influence of surgery on personal relationships, personal and professional support received and factors which were perceived to contribute to individual weight loss success or lack thereof was also assessed.

The interviews were professionally transcribed and systematically coded to identify potential themes using inductive thematic analysis (Braun and Clarke, 2014).

Statistical Analysis:

Statistical analyses were completed using IBM Statistical Package for the Social Sciences (SPSS) for windows. Continuous variables are reported as means ±SEM while categorical variables are presented as a number and percentage (n (%)) unless otherwise stated. Data were tested for normal distribution and log10 transformed where necessary. For all outcomes, available-case analysis was used. Where participants had missed an interim study visit, missing-value regression imputation was used where possible (when adjusted R2 value >0.5) to predict results rather than exclude them from analyses. One-way and two-way repeated measures Analysis of Variance (ANOVAs) were used to determine changes in overall group means (patients *vs* control participants) following gastric bypass surgery. Subsequently, Bonferonni post-hoc tests (controlling for multiple comparisons) were conducted to explore valid multiple pairwise comparisons within the dataset. Significance was considered at the p=0.05 level.

<u>Ethical considerations</u>

This study was approved by the West of Scotland Research Ethics Service (REC16/WS/0056, IRAS 200567) and registered as a clinical trial (clinicaltrials.gov; NCT03113305). To divert attention from the main purpose of the study, participants were informed that the primary purpose of the study was to measure changes in RMR following gastric bypass surgery and will be debriefed during the dissemination of study findings. Participants were fully informed of and consented to the presence of CCTV monitoring.

Personal and Public Involvement (PPI)

Patients were engaged in the design stage of the study and made valuable contributions to the study Participant Information Sheet. They were also involved in the development stage of the qualitative aspect of the study by engaging in preliminary work at 12 months to develop the questionnaire schedule to be used on the final 24month post-surgery study appointment.

Findings

Baseline Characteristics

Sixty-six participants were recruited; however, 3 patients were withdrawn from the study as they underwent a different bariatric procedure following their baseline appointment, leaving 63 participants (patients: n=31 (24F/7M), controls: n=32 (15F/17M) for inclusion. Of the patients recruited 22 (71%) underwent RYGB and 9 (29%) underwent OAGB. Baseline characteristics are presented in Table 3. There were more females in the control group than the patient group (p=0.013) which is compatible with the trend for more females electing for bariatric surgery (Buchwald, et al. 2004). The groups did not differ in age (patients: 47.3±2.1 yrs; controls: 41.1±2.4 yrs, p=0.05) but as expected the patient group had a higher BMI (patients: 45.1±1.2kg/m^2; controls: 27±0.8kg/m^2, p <0.001).

Dietary Intake

Total energy intake (EI)

Before surgery the EI of the patients was 45% higher than the control group (p=0.021; Table 4). However, by 3-months post-surgery the EI of the patients had decreased relative to both the control group (p=0.017) and baseline values (-9.93±2.67MJ/d, p<0.01). At 12-months post-surgery there was a small rebound in the EI of patients and although EI remained lower than at baseline (-6.83±2.66MJ/d, p=0.007) it was no longer significantly different from the control group (p=0.46). By 24 months EI of the patients was still 23% lower than at baseline (-5.03±3.24MJ/d) (although statistical significance had been lost (p=0.34)) but was similar to the EI of the controls (p=0.43).

Table 3 Characteristics of gastric bypass patients and control participants at baseline

	Patients (n=31)	*Controls (n=32)*	*p value*
Female n (%)	24(77.4)	15(46.9)	0.013*
Age (yrs)	47.3±2.1	41.1±2.4	0.053
Weight (kg)	122.9±4.1	78.1±2.6	<0.001*
Height (cm)	165.2±1.7	170.2±1.6	0.030*
BMI (kg/m^2)	45.1±1.2	27.0±0.8	<0.001*
BMI category	-	-	<0.001*
Normal/Underweight n (%)	0	8(25)	-
Overweight n (%)	0	17(53.1)	-
Obese n (%)	31(100)	7(21.9)	-
Diabetic at baseline n (%)	18(58.1)	0	<0.001*
T1DM	2(6.5)	0	-
T2DM	16(51.6)	0	-
Recruitment Site			
NHS England	14	-	-
Phoenix Health NI (Private)	5	-	-
Letterkenny Hospital (ROI)	12	-	-

Data expressed as mean ±SEM unless otherwise stated. Differences between continuous variables were assessed using independent sample t-tests, categorical variables were assessed using chi-square. * denotes difference (p<0.05) between groups. Abbreviations: BMI Body Mass Index; T1DM Type 1 Diabetes Mellitus; T2DM Type 2 Diabetes Mellitus; BMI category definitions: Normal/underweight <25kg/m2 Overweight 25-30kg/m2 Obese >30kg/m2. NHS England recruitment sites were Phoenix Health (NHS referred; n=10), Imperial College Hospital, London (n=1) & Southmead Hospital, Bristol (n=3)

Dietary energy density (ED)

A diet that is high in energy dense foods is often associated with obesity (Rouhani et al. 2016). However, in this study there was no difference in ED either pre- or post-surgery, with the exception that at 24 months post-surgery ED was higher in the control group than in the patients (p=0.043).

Relative macronutrient and macronutrient mix group intake

There were no differences in the relative (%EI) intake from macronutrients or macronutrient mix groups between the groups at baseline (p≥0.158) and no overall effect of surgery and time (p>0.07, (Table 4, macronutrient mix group data not shown). However, patients did consume a higher protein intake at 3- and 12-months post-surgery.

These data highlight that although patients were consuming less energy following surgery, this reduction in EI was not macronutrient specific, i.e., patients continued to eat the same foods as before surgery but in smaller portions.

Reported Food preferences

Prior to surgery, patients implied a lower desire to consume (implicit wanting) sweet foods compared to controls. Surgery and time had no overall effect on any measure of preference, liking or wanting (P≥0.508). However, between group analysis did indicate that patients had a lower preference for sweet foods preference post-surgery, with patients reporting a:

- lower expressed hedonic pleasure (explicit liking) of sweet foods at 3- and 24-months post-surgery (p<0.038),
- lower implied desire to consume (implicit wanting) of sweet foods at 3- and 12-months (p<0.001) post-surgery.

Overall, there was no change observed in any preference for fat (liking or wanting) or in actual fat intake (%EI). Although patients reduced their stated preference for sweet foods post-surgery, this was not expressed in an actual reduction in sugar intake (% EI), suggesting that that subjective food preference measures are a poor predictor of actual food intake

Table 4. Changes (mean±SEM) in energy, energy density and macronutrient intake in patient and control groups

	n	Baseline	At 3-months post-surgery	Change	1yr post-surgery	Change	2yr post-surgery	Change	ANOVA p-value
Energy Intake (MJ/d)									
Patients	16	22.3±2.9$	12.4±1.0$*	-9.9±2.7	15.4±1.1*	-6.8±2.7	17.2±1.6	-5.0±3.2	0.167
Controls	16	15.3±1.2$	15.3±0.7$	-0.1±0.9	16.6±1.4	1.3±1.2	19.3±2.1	4.0±2.0	
Energy Density (kJ/g)									
Patients	22	7.5±0.3	7.5±0.3	0.0±0.3	7.9±0.6	0.4±0.5	7.3±0.5$	0.2±0.5	0.238
Controls	23	7.7±0.4	8.1±0.4	-0.4±0.4	8.2±0.3	-0.5±0.4	8.4±0.5	-0.8±0.5	
Macronutrients									
Protein (%EI)									
Patients	16	14.6±1.0	16.1±1.2$	1.5±1.3	15.8±0.9$	1.2±1.0	14.8±1.0	0.2±1.0	0.803
Controls	16	13.1±0.6	12.4±0.6$	-0.7±0.7	13.2±0.7$	0.1±1.0	12.6±0.8	-0.5±0.8	
Fat (%EI)									
Patients	16	37.4±2.0	39.6±2.2	2.1±2.8	38.1±2.7	0.7±2.5	37.3±2.2	-0.1±2.9	0.073
Controls	16	34.4±1.9	35.6±1.4	1.2±1.2	35.1±2.4	0.7±1.8	38.1±2.2	3.7±1.9	
Saturated fat (%EI)									
Patients	16	15.9±0.9	16.8±1.2	0.9±1.5	15.2±0.6	-0.7±1.0	16.1±1.0	0.2±1.2	0.158
Controls	16	14.5±0.8	15.4±0.9	0.9±0.9	14.6±1.0	0.1±1.0	17.7±1.5	3.2±1.5	
Carbohydrate (%EI)									
Patients	16	43.7±1.5	40.6±2.6$	-3.0±2.7	41.6±2.7	-2.1±2.3	43.9±2.4	0.2±2.3	0.154
Controls	16	48.1±1.9	47.7±1.7$	-0.4±1.4	46.6±2.4	-1.5±2.2	45.1±2.6	-3.0±2.3	
Sugar (%EI)									
Patients	16	21.3±1.7	18.1±1.9	-3.2±1.9	20.0±1.6	-1.3±1.6	21.7±1.9	0.4±2.0	0.928
Controls	16	21.6±1.6	22.0±1.9	0.4±1.5	21.4±1.8	-0.1±1.6	19.3±2.1	-2.3±1.7	

Main effects assessed using two-way ANOVA (group x time). *denotes differences (p<0.05) from baseline. $denotes differences (p<0.05) between groups. **EI** Energy

Food intake behaviour

Timing of eating

When EI data were analysed by eating epoch (epoch 1: 7-11am, epoch 2: 11.01am-3pm, epoch 3: 3.01–7pm, epoch 4: 7.01-11pm), no differences emerged in the circadian patterning of EI across the day either between or within the patient and control groups at any time (p=0.776).

Changes in eating patterns

There were no differences in any measures of eating patterns i.e., frequency, duration, speed or energy content, between the groups at baseline (P>0.394).

However, by 3 months post-surgery patients were managing their food intake by eating more frequently, but simultaneously reducing their EI by eating smaller amounts of food (MJ, g) at a slower rate (g/min). However, by 12 months eating rate had started to increase and at 24 months the number of eating occasions at returned to a frequency similar to pre-surgery. However, the size of EO (MJ) remained lower than pre-surgery across all time points.

Table 5. Changes in eating behaviour of patient and control groups

Behaviour parameter		**Baseline**	**3 months**	**12 months**	**24 months**	*ANOVA P value*
Number of EO (n)						
Patients	25	9±0.6	10±0.5*	11±0.8*	6±0.5	0.021
Controls	25	9±0.6	8±0.5	9±0.5	5±0.3*	
Time /EO (min)						
Patients	11	21±3.0	14±1.4	13±1.6	13±2.4	0.48
Controls	10	20±3.8	17±1.10	15±2.1	14±2.1	
MJ / EO						
Patients	17	3±0.3	1±0.2$*	2±0.1*	2±0.2*	0.005
Controls	18	3±0.31	3±0.4$*	2±0.3*	3±0.2*	
g / EO						
Patients	11	582±51.7	276±39.9$*	371±41.0	363±72.5*	0.21
Controls	10	610±113.8	440±104.7$	425±61.9	408±50.1	
kJ/min						
Patients	14	169±25.9	101±10.1	131±19.8	157±15.1	0.10
Controls	18	173±12.1	151±22.1	143±19.2	192±12.9	
g/min						
Patients	14	31±3.6	21±1.6$	27±2.8	29±2.6	0.07
Controls	18	37±2.2	29±2.6$*	31±4.5	33±2.2	

Results from two-way ANOVA (group x time). *denotes significant (p<0.05) change from baseline. $denotes significant (p<0.05) between-group difference. **EO** Eating Occasion

Changes in body composition

By 1year post-surgery patients had lost over a quarter (25.4%; p<0.001) of their initial body weight, with only a small rebound at 24 months post-surgery and this weight loss was largely retained at 24 months post-surgery (23.8%; p<0.001). In contrast the control group remained weight stable (p=1.00).

The relative contribution of FM, LM and VF to total body mass in the patient group changed over time (Figure 2). At 12-and 24 months patients had lost a fat to lean ratio of approximately 4:1, equating to a loss of 45.0% of their body fat mass but only 11.2% of their LM at 12 months. At 24 months this equated to 43.0% loss in fat mass and 12.2% of their LM. This transition in fat: lean mass ratio is higher than what is generally achieved with other weight loss interventions (3:1), although the latter varies widely (Heymsfield et al 2014).

The relative contribution of FM, LM and VF to body mass in the control group did not change over time with FM increasing by 4.2% and LM by 1.8% over the duration of the study.

These data on body composition indicate that patients lose proportionately more fat mass post-gastric bypass surgery while LM is better preserved. This effect will have a positive impact on RMR, as LM is its major determinant, helping patients maintain energy balance.

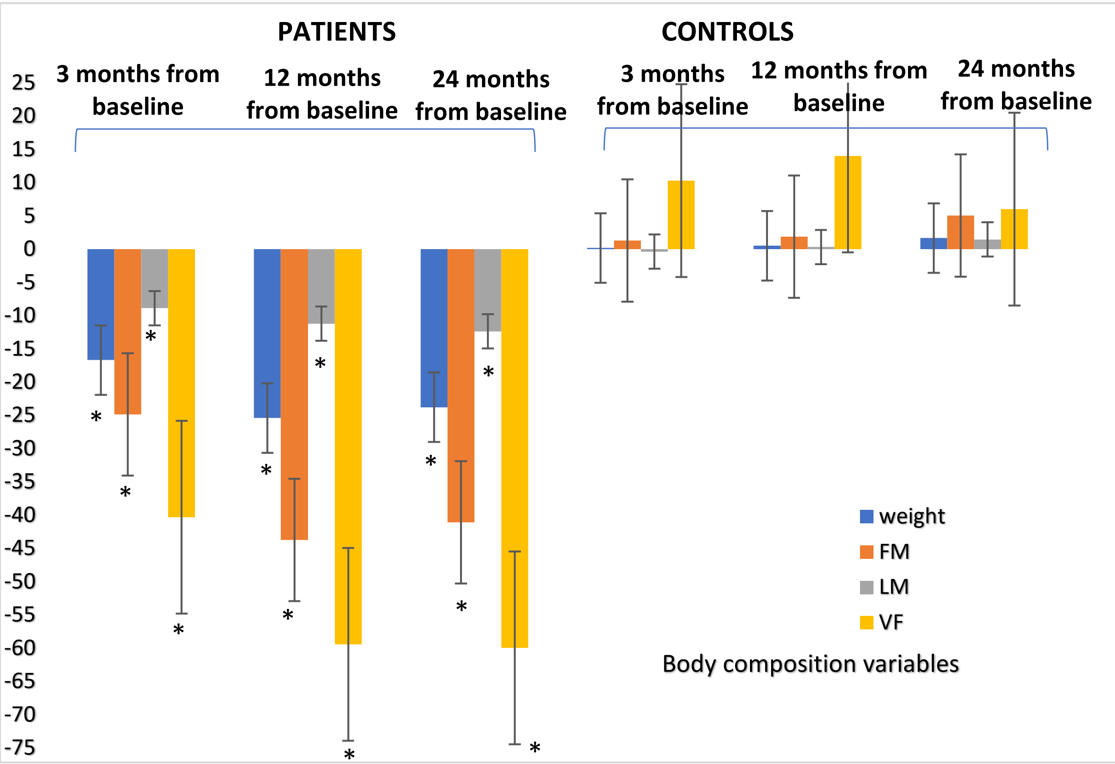


Figure 2. Change (%) in body composition in patients and controls. FM, fat mass; LM, lean ass; VF, visceral fat. *denotes change (p<0.05) from baseline. Two-way ANOVA between groups (total weight, p<0.005; FM, p<0.001; LM, p<0.001; VF, p<0.001)

Energy expenditure

Total Energy Expenditure (TEE)

Given the small number of patients whose TEE was assessed by DLW it was not possible to impute values for missing timepoints (COVID-19 related), leaving only 3 complete participant datasets. Overall TEE increased from baseline (Table 6).

Resting Metabolic Rate (RMR)

A reduction in the RMR of the patients (kJ/KgLM) was observed over time post-surgery ($p<0.003$). This can be accounted for by the post-operative weight loss, particularly the loss of LM which is the strongest driver of RMR. Interestingly, when expressed per kg body weight RMR increased (albeit non-significantly) at 12- (+3.3%) and 24-months (+7.6%) post-surgery perhaps reflecting the preservation of LM.

Energy Cost of Physical Activity (PAL)

Statistical analysis of the cost of physical activity was not conducted as there was only 3 complete patient datasets. However, the limited data available indicate that the physical activity level (PAL (TEE/RMR)) of the patients increased after surgery.

These data on energy expenditure indicate that the RMR of the patients reduces after surgery, reflecting their loss in body weight. However, this reduction may be offset to some extent by the retention of LM (the strongest driver of RMR) in patients post-surgery. In addition, the lower RMR may be compensated for, at least in part, by an increase in physical activity post-surgery resulting in an overall higher TEE.

Medication Information

At baseline, 18 patients were taking either prescribed antidiabetic, anti-hypertensive and/or lipid-lowering medications. By 24-months post-surgery only six patients required the same dosage of medication that they took at baseline. All other patients either reduced dosage or discontinued the use of one or more medications.

Table 6: Changes in energy expenditure measures (mean ±SEM) in patient post-gastric bypass surgery

		Baseline	3-mths post-surgery	Change	1yr post-surgery	Change	2yr post-surgery	Change	p-value
RMR (MJ/d)									
Patients	17	10.3±0.7$	7.8±0.5*	-2.5±0.5	7.3±0.5*	-3.0±0.6	7.5±0.6$*	-2.8±0.9	0.160
Controls	13	6.9±0.5$	7.1±0.4	0.2±0.4	6.5±0.4	-0.4±0.4	6.5±0.2$	-0.4±0.3	
RMR (kJ/kg)									
Patients	24	80.8 ±4.3	76.4 ±3.7$	-4.5 ±2.6	81.9 ±4.7	1.1 ±3.6	83.4 ±4.8	2.6 ±5.2	0.484
Controls	13	99.4 ±6.9	103.0 ±5.4$	3.7 ±4.8	89.8 ±3.3	-9.5 ±6.1	93.6 ±4.4	5.7 ±4.2	
RMR (kJ/kgLM)									
Patients	17	174.9±11.8	146.1±9.7*	28.8±7.2	140.7±10.1	-34.2±9.4*	145.7±12.1	29.2±15.3	0.212
Controls	13	155.3±9.4	162.4±7.8	7.1±7.5	142.3±5.8	-13.0±9.5	146.5±5.7	-8.8±6.9	
TEE (MJ/d)									
Patients	3	7.5±3.1	10.4±1.4	2.9±2.7	9.6±0.7	2.1±3.8	8.9±0.2	1.4±3.3	0.801
Total energy cost of PA (PAL)									
Patients	3	0.9±0.4	1.5±0.4	1.4	1.6±0.2	1.2±0.4	1.3±0.1	0.5±0.5	-

Main effects assessed using two-way ANOVA (group x time) and Friedman's test for non-normal data (n=3). Change indicates change from baseline values. Data considered significant at the p<0.05 level. *denotes differences (p<0.05) from baseline. $denotes differences (p<0.05) between groups. RMR; resting metabolic rate, TEE; Total Energy Expenditure (measured by doubly labelled water)

Qualitative Findings

Three main themes emerged from the qualitative data (changes in eating behaviour; factors influencing patient satisfaction; factors that influence weight regain) from which further subthemes were identified (Figure 3).

Changes in eating practices	Factors influencing patient satisfaction	Factors influencing weight regain
• Eat less • Eat to live • Eat to feel better, • Eat what I cook • Dislike what I used to like	• Weight loss, • Health improvements, • Support network • Information/ preparation • Expectations • Surgical care	• Old habits die hard • Lack of clinical support

Figure 3. Issues emerging from qualitative discussions with patients 24-months after gastric bypass

Patients reported adjusting their eating post-surgery in a number of ways (Figure 3) and generally had a more positive attitude towards food, perhaps driven by their weight loss and the overall health benefits experienced. It was interesting to compare these outcomes with the quantitative study outcomes, noting that patients reported eating less 'Eat less' and a change in food preferences 'Dislike what I used to like'. Overall patients also talked positively about their surgery, identifying their support network (clinical team, family/friends/work colleagues) as key players in helping to meet their expectations and therefore impacting on the satisfaction with their surgery.

Of concern, however, is that the positive eating practices adopted following surgery, might not be maintained in the longer term through the admission of the patients that 'old habits die hard' and how a lack of clinical support from dietitians, counsellors etc. may have contributed to some weight regain in the longer term. Patients admitted feeling left to manage their diet alone when they felt they would benefit from more input from dieticians and counselling to overcome these hurdles.

There is a direct link between individualised care and patient satisfaction which, in turn, may significantly impact on the prevention of weight regain. Longer-term personally tailored advice from health professionals is recommended to reinforce positive eating practices and support positive changes to the patient's health and wellbeing.

Key findings and Conclusion

- Before surgery the patients had a greater EI than the control group (45% more), but there was no difference in the **relative contributions of macronutrients** to EI.
- Following gastric bypass patients consumed 21.5% **less energy** (6.83MJ/d less at 12 months post-surgery) but were eating more frequently
- Despite an indication of a **reduced preference** for sweet food there was no change in the relative contributions of macronutrients consumed post-surgery, indicating that the **same foods** were being consumed but in **smaller amounts**.
- Patients achieved a maximum total **body weight loss of 25%** with a 4:1 ratio of fat to lean mass loss at 12 post-surgery. In contrast, the relative contribution of LM to total body mass in the control group remained stable over time.
- The expected **decrease in RMR** of the patients as a result of weight loss was **offset to some extent by the maintenance of LM post-surgery**. In addition, the lower RMR may be compensated for, at least in part, by an increase in physical activity post-surgery resulting in an overall **higher energy expenditure**. However, this work was only conducted on a small number of patients.
- Two thirds of patients requiring obesity-related medications (e.g., antidiabetic, anti-hypertensive, lipid-lowering) had reduced or no longer required these **medications** by 24-months post-surgery.
- Qualitative data highlighted a direct association between **individualised clinical care** and patient post-surgery satisfaction and prevention of weight regain.

This study is the first to objectively measure food intake across multiple eating occasions in patients after gastric bypass surgery. The findings concur with outcomes from an earlier Danish study where objective measurements were taken in a bariatric surgery population during a single eating occasion (Nielsen et al., 2017; Nielsen et al., 2018).

A robust methodology to assess the various components of eating and other associated behaviours is imperative for understanding the causal mechanisms underlying changes in food intake after bariatric surgery. While this unique study design represented a compromise between the demands of external and internal validity it has filled a critical void in understanding the dynamics of food selection and intake behaviour following bariatric surgery which, hitherto, has suffered from overreliance on and uncritical acceptance of the purported integrity of self-reported food intake data.

Practice and Policy Implications/Recommendations/Pathways to Impact

Understanding the underlying mechanisms and postoperative eating behaviours that contribute to individual variability in the reduction of EI and body weight following surgery could help identify those who are most likely to benefit from gastric bypass surgery and provide more individually targeted approaches to optimise the treatment and management of obesity and type 2 diabetes. It may also have the potential to inform the development of more targeted approaches for the majority of people with obesity/ type 2 diabetes who will manage the condition by non-surgical treatments and allow patients to make more informed decisions regarding their treatment approaches.

This unique study protocol and the employment of robust fit-for purpose experimental tools also presents a unique opportunity to gain a further, deeper understanding of the **long-term** dynamics of food intake, food preferences and weight trajectory by following up this well-characterised cohort at 5 years post-surgery.

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