Investigating the Effects of Different Weight Loss Interventions on Eating Behaviour and Reward-Driven Eating in Patients with Obesity and Type 2 Diabetes

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A Thesis Submitted for the Degree of Doctor of Philosophy

In the Department of Metabolism, Digestion and Reproduction

Faculty of Medicine

Imperial College London

2021

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"Love and knowledge, so far as they were possible, led upward toward the heavens. But always pity brought me back to earth. Echoes of cries of pain reverberate in my heart. Children in famine, victims tortured by oppressors, helpless old people a hated burden to their sons, and the whole world of loneliness, poverty, and pain make a mockery of what human life should be. I long to alleviate the evil, but I cannot, and I too suffer."

– *Bertrand Russell*

ABSTRACT

Obesity has become a global health issue, and type-2 diabetes (T2DM) is one of its most common comorbidities. The Roux-en-Y gastric bypass (RYGB) is the most effective surgical procedure for treating obesity, resulting in significant and sustainable weight loss. One proposed mechanism for how RYGB achieves successful weight-loss is based on profound changes in the secretion of gastrointestinal hormones that follow surgery, including increases in Glucagon-Like Peptide-1, Oxyntomodulin and Peptide YY (GOP). Surgically induced changes in physiology are also associated with specific behavioural factors and psychological characteristics, both of which are recognised as important contributors to successful postoperative outcome. This study hypothesised that patients with obesity and T2DM following RYGB have a healthier eating behaviour profile, mediating the long-term sustainable weight loss than Very-Low-Calorie diet (VLCD) or GOP infusion. Eating behaviour, food reward, psychological status, health-related quality of life and food intake were assessed at baseline and following each intervention using a set of validated questionnaires and a 4-day food-diary before and after each intervention. The RYGB showed a reduction in the reward drive to eat at three-month which was maintained up to one-year post-surgery. There were also reductions in external-eating, disinhibition and weight and shape concerns which were not observed following VLCD or GOP, suggesting that calorie-restriction or gut-hormone alone maybe not be responsible for changes in eating behaviour following RYGB. Meanwhile, there were similarities between the RYGB and GOP groups in terms of the increase in the flexible dietary restraint measured by the Dutch Eating Behaviour questionnaire. Moreover, the GOP group did not show any changes in the taste perception as were observed following RYGB. Understanding the behavioural mechanisms that account for such variations could help the development of personalised therapeutic approaches based on the need to improve treatment outcomes and dietary advice offered to patients with obesity.

TABLE OF CONTENTS

ABSTRACT **1**

LIST OF FIGURES **6**

LIST OF TABLES **7**

ACKNOWLEDGEMENTS **8**

STATEMENT OF WORK BY CANDIDATE **9**

COPYRIGHT DECLARATION **10**

PUBLICATIONS RELATING TO THIS THESIS **11**

ABSTRACTS AND PRESENTATIONS RELATING TO THIS THESIS **11**

ABBREVIATIONS USED IN THIS THESIS **14**

GLOSSARY **15**

1. CHAPTER ONE: LITERATURE REVIEW **16**

1.1. THE BURDEN OF OBESITY AND TYPE 2 DIABETES 17
1.1.1. Obesity *17*
1.1.2. Potential causes of obesity *18*
1.1.2.1. Biological factors *18*
1.1.2.1.1. The effects of genetic factors on body weight *20*
1.1.2.1.2. The effects of stress on body weight *21*
1.1.2.2. Psychological factors *22*
1.1.2.2.1. Restraint and disinhibition eating *22*
1.1.2.2.2. Emotional and external eating *25*
1.1.2.2.3. Mental health problems *27*
1.1.2.3. Environmental factors *27*
1.1.3. Type 2 diabetes *28*
1.1.4. Currently available treatments for obesity *29*
1.1.4.1. Lifestyle and weight management modification *29*
1.1.4.1.1. Calorie restriction and very low-calorie diets *30*
1.1.4.2. Pharmacotherapy for obesity *32*
1.1.4.3. Bariatric surgery *35*
1.1.4.3.1. Laparoscopic Adjustable Gastric Banding (LAGB) *35*
1.1.4.3.2. Vertical Sleeve Gastrectomy (VSG) *36*
1.1.4.3.3. Roux-en-Y Gastric Bypass (RYGB). *36*
1.1.4.4. Bariatric surgery and weight loss *38*
1.1.4.5. Bariatric surgery and type 2 diabetes *38*
1.1.4.6. Mechanisms mediating weight loss in RYGB *39*
1.1.4.6.1. Evidence for gastric and calorie restriction *40*
1.1.4.6.2. Evidence for gut hormones *40*
1.1.4.6.2.1. Glucagon-Like Peptide-1 (GLP-1) *41*
1.1.4.6.2.2. Oxyntomodulin (OXM) *42*
1.1.4.6.2.3. Peptide YY3-36 (PYY_{3-36}) *43*
1.1.4.6.3. Evidence of satiety *44*
1.1.4.6.4. Evidence for changes in food preference *44*
1.1.4.6.5. Evidence for change in taste *46*
1.1.4.6.5.1. Taste system *46*
1.1.4.6.5.2. Taste changes after RYGB *47*
1.2. SUMMARY OF INTRODUCTION AND RELEVANCE TO THESIS 50
1.2.1. Overall aims of this thesis *52*
1.2.2. Hypotheses *52*
1.2.3. Chapters summaries *53*

2. CHAPTER TWO: MATERIALS AND METHODS 55

2.1. RECRUITMENT OF TRIAL PARTICIPANTS 57
2.1.1. Inclusion and exclusion criteria 57
2.2. OUTCOME MEASURES 59
2.3. STUDY PROTOCOL 59
2.3.1. RYGB study 60
2.3.2. VLCD study 60
2.3.3. Infusion study 61
2.4. DATA COLLECTION AND PREPARATION 65
2.4.1. Questionnaire data 65
2.4.1.1. Eating and behaviour questionnaires 65
2.4.1.1.1. The Dutch Eating Behaviour Questionnaire (DEBQ) 65
2.4.1.1.2. Three-Factor Eating Questionnaire (TFEQ) 66
2.4.1.1.3. Eating Disorder Examination Questionnaire (EDE-Q) 67
2.4.1.2. Food reward questionnaire 68
*2.4.1.2.1. Power of Food Scale (**PFS**) 68*
2.4.1.3. Psychological status questionnaires 69
2.4.1.3.1. The Beck Depression Inventory (BDI-II) 69
2.4.1.3.2. Behavioural Inhibition and Activation System (BIS/BAS) scales 69
2.4.1.3.3. Hospital Anxiety and Depression Scale (HADS) 70
2.4.1.3.4. Barratt Impulsivity Scale (BIS) 71
2.4.1.4. Health-related quality of life (HR-QoL) Questionnaires 72
2.4.1.4.1. Short-Form 36 Health Survey Questionnaire (SF36) 72
2.4.1.4.2. Impact of Weight on Quality of Life-Lite (IWQOL-Lite) 73
2.4.1.5. Behavioural change questionnaires 74
2.4.1.5.1. Alcohol Use Disorders Identification Test (AUDIT) 74
2.4.2. Dietary food record 75
2.4.3. Taste test data 76
2.4.4. Anthropometric measurements 81
2.4.5. Glycaemic management 82
2.5. STATISTICAL ANALYSIS 83
2.5.1. For within-group comparisons 83
2.5.2. For between-group comparisons 83

3. CHAPTER THREE: ROUX-EN-Y GASTRIC BYPASS 87

3.1. INTRODUCTION 88
3.2. RESEARCH AIM 91
3.3. RESEARCH HYPOTHESES 91
3.4. METHODOLOGY 92
3.4.1. Questionnaire data 92
3.4.2. Food intake data 95
3.4.3. Statistical data analysis 95
3.5. RESULTS 96
3.5.1. Participant characteristics for the RYGB questionnaires data 96
3.5.2. Eating behaviour following RYGB 99
3.5.3. Reward Drive to Eat following RYGB 100
3.5.4. Psychological and behavioural changes following RYGB 102
3.5.5. Health-related quality of life following RYGB 104
3.6. Changes in food intake based on dietary records following RYGB 106
3.7. Anthropometric data following RYGB 108
3.8. DISCUSSION 110
3.8.1. Summary of findings for RYGB 110
3.8.2. Reward drive to eat and food intake following RYGB 110
3.8.3. Eating behaviour following RYGB 114
3.8.4. Psychological status following RYGB 123
3.8.5. Health-related quality of life following RYGB 124
3.8.6. Alcohol consumption following RYGB 124
3.9. CONCLUSION OF RYGB STUDY 126
3.10. LIMITATIONS 126

4. CHAPTER FOUR: VERY-LOW-CALORIE DIET 129

4.1. INTRODUCTION 130
4.2. RESEARCH AIM 132
4.3. RESEARCH HYPOTHESES 132
4.4. METHODOLOGY 133
4.5. STUDY PROTOCOL 133
4.5.1. Questionnaire data *134*
4.5.2. Food intake data *136*
4.5.3. Statistical analysis *137*
4.6. RESULTS 138
4.6.1. Participant characteristics for VLCD questionnaire data *138*
4.6.2. Eating behaviour following VLCD *140*
4.6.3. Food reward following VLCD *141*
4.6.4. Psychological and behavioural questionnaires following VLCD *142*
4.6.5. Health-related quality of life following VLCD *149*
4.6.6. Changes in food intake based on dietary records following VLCD *154*
4.6.7. Anthropometric data *156*
4.7. DISCUSSION 158
4.7.1. Summary of the findings for VLCD *158*
4.7.2. Eating behaviour following VLCD *158*
4.7.3. Reward drive to eat following VLCD *159*
4.7.4. Psychological status, alcohol consumption and quality of life following VLCD *161*
4.8. CONCLUSION OF VLCD STUDY 162
4.9. LIMITATIONS 162

5. CHAPTER FIVE: INFUSION STUDY (PART 1) 163

5.1. INTRODUCTION 164
5.2. RESEARCH AIM 168
5.3. RESEARCH HYPOTHESES 168
5.4. METHODOLOGY 168
5.4.1. Study protocol *169*
5.4.2. Outcome measures *171*
5.4.3. Questionnaire Data *172*
5.4.4. Food intake data *174*
5.4.5. Statistical data analysis *175*
5.5. RESULTS: 176
5.5.1. Participant characteristics *176*
5.5.2. Demographics Data *177*
5.5.3. Questionnaire Data *177*
5.5.3.1. Eating behaviour questionnaires following GOP infusion *179*
5.5.3.2. Reward drive to eat following GOP infusion *181*
5.5.3.3. Psychological and behavioural changes following GOP *191*
5.5.4. Changes in food intake based on dietary records following GOP infusion *207*
5.5.5. Anthropometric data following GOP infusion *213*
5.6. DISCUSSION 217
5.6.1. Summary of the infusion group findings *217*
5.6.2. Reward drive to eat and food intake following GOP infusion *218*
5.6.3. Eating behaviour following GOP infusion *219*
5.6.4. Psychological status following the infusion *225*
5.6.5. Weight-related quality of life following the infusion *225*
5.6.6. Food intake following the infusion *226*
5.7. Conclusion of GOP infusion study *228*
5.8. Limitations *228*

6. CHAPTER SIX: INFUSION STUDY (PART 2) 229

6.1. INTRODUCTION 230
6.2. RESEARCH AIM 233
6.3. RESEARCH HYPOTHESES 233
6.4. METHODOLOGY 234

6.4.1. Statistics ... *235*
6.5. RESULTS ... 237
6.5.1. Sweet taste detection threshold ... *237*
6.5.2. Sweet taste intensity ... *240*
6.5.3. Consummatory reward value of sweet taste ... *240*
6.6. DISCUSSION ... 242
6.6.1. Summary of GOP findings ... *242*
6.7. LIMITATIONS ... 248

7. CHAPTER SEVEN: GENERAL DISCUSSION ... 249

7.1. SUMMARY OF MAIN FINDINGS ... 250
7.2. CONCLUDING COMMENTS ... 257
7.3. CONCLUSION ... 258
7.4. LIMITATIONS AND FUTURE DIRECTIONS ... 262
7.4.1. LARGER LONGITUDINAL STUDIES ... 262
7.4.2. COMPARISON OF BEHAVIOURAL DATA WITH NEUROIMAGING DATA ... 263
7.4.3. USING QUALITATIVE QUESTIONERS ... 263
7.4.4. USE OF BIOLOGICAL MARKERS TO VALIDATE SELF-REPORTED DIETARY INTAKE ... 263
7.4.5. FURTHER INVESTIGATION OF OTHER RYGB MECHANISMS ... 264
7.5. THE IMPORTANCE OF LANGUAGE IN THE FIELD OF OBESITY ... 265

REFERENCES & APPENDICES ... 268

REFERENCES ... 269
APPENDICES ... 323

LIST OF FIGURES

Figure 1: *Summary of the influence Restraint and Disinhibition have upon obesity* *24*

Figure 2: *Anatomy of the 3 most common bariatric procedures* *37*

Figure 3: *A Canè Crono pump and a Medtronic infusion set* *64*

Figure 4: *Study visit plan for the group interventions* *85*

Figure 5: *Consort diagram of patient entry into studies* *86*

Figure 6: *Gastric bypass surgery (RYGB)* *90*

Figure 7: *Effects of RYGB on body weight and BMI throughout the study* *109*

Figure 8: *Effects of VLCD on body weight and BMI throughout the study* *157*

Figure 9: *Effects of GOP on body weight and BMI throughout the study* *216*

Figure 10: *Corrected Hit Rates from the Sweet Taste Detection Threshold Tests* *239*

Figure 11: *Intensity and consummatory reward value of sweet taste assessed by gLMS, VAS, and JAR* *241*

LIST OF TABLES

Table 1: *Past and current anti-obesity drugs* *34*

Table 2*: Baseline characteristics of the RYGB participants* *98*

Table 3: *Eating behaviour and food reward questionnaires following RYGB* *101*

Table 4: *Psychological and behavioural questionnaires following RYGB* *103*

Table 5: *Quality-of-life questionnaires following RYGB* *105*

Table 6: *Changes in food, alcohol and macronutrient composition intake following RYGB* *107*

Table 7: *Changes in body weight following RYGB* *108*

Table 8: *Baseline characteristics of studied participants (VLCD/RYGB)* *139*

Table 9: *Eating behaviour and food reward following VLCD/RYGB* *143*

Table 10: *Psychological and behavioural status following VLCD/RYGB* *146*

Table 11: *Quality-of-life questionnaires following VLCD/RYGB* *150*

Table 12: *Changes in food, alcohol and macronutrient composition intake following VLCD* *155*

Table 13: *Changes in body weight following VLCD* *156*

Table 14: *Baseline characteristics of studied participants (GOP/Saline/RYGB)* *178*

Table 15: *Questionnaire scores at baseline across all interventions* *182*

Table 16: *Continued questionnaire scores at baseline across all interventions* *184*

Table 17: *Eating behaviour and food reward following GOP/Saline* *185*

Table 18: *Eating behaviour and food reward following GOP/RYGB* *188*

Table 19: *Psychological and behavioural status following GOP/Saline* *192*

Table 20: *Psychological and behaviour status following GOP/RYGB* *195*

Table 21: *Quality-of-life following GOP/Saline* *199*

Table 22: *Quality-of-life following GOP/RYGB* *203*

Table 23: *Baseline food intake data across all intervention groups* *208*

Table 24: *Changes in food, alcohol and macronutrient composition intake following GOP/Saline* *209*

Table 25: *Changes in food, alcohol and macronutrient composition intake following GOP/RYGB* *211*

Table 26: *Changes in body weight across interventions* *214*

Table 27: *Change in percentage body weight across interventions* *215*

Table 28: *Baseline characteristics of the studied participants (GOP/Saline)* *238*

Table 29: *Summary of findings* *260*

ACKNOWLEDGEMENTS

First and foremost, thank **Allah** who *"Has taught man that which he knew not"* for giving me strength and the ability to complete this work and in bringing this research project to fruition.

My gratitude goes to my supervisors, under whose guidance, I have improved immeasurably as a scientist and as a communicator; **Professor Tricia** Tan for her enduring guidance, and for always providing me with challenging opportunities, and support that helped me rise to meet them; **Dr Samantha** Scholtz for all for being a supportive supervisor, not just in academic terms, but pastorally too, helping me to navigate all the pressure and deadlines; **Professor Gary** Frost for his encouragement and scientific mentorship.

I would like to thank the practical, judicious, efficient, supportive, inspiring, and best career mentor I could ask for, **Dr Saira** Hameed, for her camaraderie and for mentoring me, not only in science but also in life. I am excited to keep learning from her every day.

I would like to thank my team members, starting with **Dr George** Tharakan and **Dr Preeshila** Behary for providing invaluable support and guidance from day one at the CRF of Imperial College London and throughout my PhD; **Dr Julia** Kenkre, and **Dr Sirazum** Choudhury for how inspirational and supportive they have been; and thank you for the rest of my team who are equally kind, fiercely intelligent and fun: **Dr Kleopatra** Alexiadou, **Dr David** Hope, **Dr Yemi** Ilesanmi, **Dr Oluwaseun** Anyiam, **Dr Ankur** Poddar, **Mrs Chedie** Doyle, **Mr Ahmad** Rabie and **Dr Khalefah** Malallah for giving me the greatest PhD training environment and experience I could ask for! Thanks also to **Dr Nichola**s Johnson for answering all my statistical questions and **Dr Rachel** Gibson for training me on the Airwave protocol. My special thanks to the patients and participants who took part in this study.

I would also like to thank my friends **Abrar B, Alia, Amjad&Banan J, Brett, Essra N, Ghada D**, **Ghada&Hanadi**, **Hessa**, **Madhawi, Mai Gh, Mai Kh**, **Midad**, **Sara H, Sara N, Shahd, Shukri, Souad, Sofeya AS** and **Tory** for their advice, support, and interest in my research.

Lastly, my heartfelt love and thanks go to my father **Dakhailallah** for his ability to inspire growth in me, and for constantly setting the standard so high; my mother **Raya** Al Nefaie for always believing in me and supporting me, all my beloved **brothers**, **sisters**, and my **sisters-in-law** who have been consistently and unerringly supportive. I cannot express enough my gratitude to my brother **Rakan** for his unwavering support and encouragement since I started my study in London; to **Auntie Rasha, Mohammed, Rami, Mansour, Abdullah, Jasser, Khaled, Morooj and Hala** for providing absolute support during my write-up and my whole journey.

With my heartfelt gratitude, THANK YOU all.

STATEMENT OF WORK BY CANDIDATE

All the work described in the thesis was performed by the author. Human studies including recruitment, scanning, and data collection were performed in collaboration with **Dr George Tharakan, Dr Preeshila Behary, Dr Kleopatra Alexiadou, Dr Julia Kenkre, Dr Sirazum Choudhury, Dr David Hope, Dr Yemi Ilesanmi, Dr Oluwaseun Anyiam, Dr Ankur Poddar, Mrs Chedie Doyle, and Mr Ahmad Rabie**. Taste data analysis was performed in collaboration with **Dr Madhawi Aldhwayan**

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ABBREVIATIONS USED IN THIS THESIS

ANOVA	**An**alysis **o**f **V**ariance
AUD	**A**lcohol **U**se **D**isorder
BAND	Gastric **Band**ing
BMI	**B**ody **M**ass **I**ndex
CNS	**C**entral **N**ervous **S**ystem
COVID-19	**Co**rona**vi**rus **D**isease 20**19**
DEBQ	**D**utch **E**ating **B**ehaviour **Q**uestionnaire
DiRECT	**Di**abetes **Re**mission **C**linical **T**rial
DPP-4	**D**ipeptidyl **Pe**ptidase **IV**
EMA	**E**uropean **M**edicines **A**gency
FDA	**F**ood and **D**rug **A**dministration
FM	**F**at **M**ass
fMRI	**f**unctional **M**agnetic **R**esonance **I**maging
gLMS	**g**eneralized **L**abelled **M**agnitude **S**cale
HADS	**H**ospital **A**nxiety and **D**epression **S**cale
IV	**I**ntra**v**enous
GCGR	**G**luca**g**on **R**eceptor
GLP-1	**G**lucagon-**l**ike **P**eptide-**1**
GLP-1R	**G**lucagon-**l**ike **P**eptide-**1 R**eceptor
GOP	A combination of triple gut hormones (**G**LP-1, **O**XM, **P**YY$_{3-36}$)
JAR	**J**ust **A**bout **R**ight
LAGB	**L**aparoscopic **a**djustable **g**astric **b**anding
MC4R	**M**elano**c**ortin-**4 r**eceptor
PFS	**P**ower of **F**ood **S**cale
NICE	The **N**ational **I**nstitute for Health and **C**are **E**xcellence
NPY	**N**euro**pe**ptide **Y**
OFC	**O**rbito**f**rontal **c**ortex
OXM	**O**xynto**m**odulin
Pmol/kg/min	**P**ico**mol**e Per **K**ilo**g**ram Per **M**inute
POMC	**P**roo**p**io**m**elano**c**ortin
PYY	**P**eptide **Y**rosine **Y**rosine
REE	**R**esting **E**nergy **E**xpenditure
RYGB	**R**oux-en-**Y G**astric **B**ypass
SC	**S**ub**c**utaneous
SEM	**S**tandard **e**rror of the **m**ean
SOS	**S**wedish **O**bese **S**ubjects
T2DM	**T**ype **2 D**iabetes **M**ellitus
TFEQ	**Three-Factor E**ating **Q**uestionnaire
UK	**U**nited **K**ingdom
VAS	**V**isual **A**nalogue **S**cale
VLCD	**V**ery **l**ow-**c**alorie **d**iet
VSG	**V**ertical **S**leeve **G**astrectomy

GLOSSARY

Term	*Meaning in this thesis*
A Low-Calorie Diet	Diet plan that involves eating between 800 and 1,500 calories a day
A Very Low-Calorie Diet	Diet plan that involves eating 800 calories a day
Anorexigenic Gut Hormones	Hormones that reduce appetite, resulting in lower food consumption, leading to weight loss such as Glucagon-Like Peptide
Class-3 Obesity	A body mass index over 40 kg/m^2 (severe obesity)
Cognitive Restraint	Conscious attempts to control and monitor food intake to achieve optimal weight
Detection Threshold	The lowest concentration at which a taste solution can be distinguished from water
Disinhibition (Eating)	Loss of control overeating and consequent overconsumption of calories
Eating Behaviour	A broad term that encompasses food choice and motives, feeding practices, and some eating traits such as emotional and external eating
Emotional Eating	Eating in response to (usually) negative emotions such as anxiety and depression, although other emotions such as happiness or boredom can also be triggers, as opposed to internal hunger cues
External Eating	Eating in response to external stimuli – including the sight, smell, sound, or taste of palatable food – as opposed to internal cues such as hunger
Gut-brain axis	A bidirectional communication that connects the central and enteric nervous systems, connecting the brain's emotional and cognitive centres of the brain with peripheral intestinal activity.
Reward Drive to Eat/ Reward-Driven Eating	The drive to eat to derive pleasure or reward from food as opposed to eating in response to internal hunger cues
Liking	An observable reward response that can be detected neurally or behaviourally and is often followed by a subjective experience.
Obesity	The excessive accumulation of body fat that presents a risk to health which measured by a body mass index of above 30 kg/m^2 [8]
Obesogenic Environment	Environmental factors (i.e. the surroundings, opportunities, or conditions of life) that result in over-nutrition and reduced physical activity which promote obesity in individuals and populations [9]
Orexigenic Gut Hormone	An appetite stimulant hormone (Ghrelin)
Overweight	A body mass index of 25 to 29.9 kg/m^2
Restraint (Eating)	The intention to restrict food intake deliberately to prevent weight gain or to promote weight loss
Taste Sensitivity	The minimum concentration at which a specific taste quality can be perceived
Wanting	The conditioned incentive salience or motivation for reward elicited by reward-related cues, which is often followed by subjective desires.

1. CHAPTER ONE:

LITERATURE REVIEW

1.1. The burden of obesity and type 2 diabetes

1.1.1. Obesity

Obesity represents one of the world's most important public health issues, and its incidence is rapidly growing. If current trends continue, 38% of the world's adult population will be **overweight** and another 20% will have obesity by 2030 (10). In the **UK**, figures have increased four-fold over the last 30 years, from 6% in 1983 to 27% today. This means that more than a quarter of **UK** adults are now living with obesity (11). Obesity is defined as the excessive accumulation of body fat that presents a risk to health (8). Globally there has been an increase in the consumption of high energy palatable foods, which are generally high in sugar and processed fat and are strongly linked with obesity (12). In the body, excess energy intake in form of sugar and fat is converted to triglyceride and stored in adipose tissue depots that expand in size to increase body fat and cause weight gain. The most widely used measure of obesity is the body mass index (**BMI**) (13). Obesity is associated with a variety of physical and mental health co-morbidities such as type 2 diabetes mellitus (**T2DM**) (14), cardiovascular diseases (14, 15), obstructive sleep apnoea, depression, dementia (16) and several types of cancer (17), all of which have adverse effects on the quality of life, morbidity and mortality, work productivity, and healthcare costs. All health risks are shown to diminish significantly when modest weight loss (as low as 5%) is achieved. Moreover, since the earlier days of the COVID-19 pandemic, multiple studies and several systematic reviews and meta-analyses have confirmed obesity as a risk factor for worse outcomes during **COVID-19** infection (18-22). Recently, a very large community-based cohort study found that a BMI of above 23 kg/m^2 was linearly associated with an increased risk of severe **COVID-19**, leading to hospital admission and death, especially in those under 40 years(23). In another study of health risk factors associated with **COVID-19** mortality among approximately half a million people in Mexico,

obesity was found to be a specific risk factor for COVID-related mortality and to cause a higher risk of complications and adverse outcomes (24).

1.1.2. Potential causes of obesity

The epidemiology of obesity is complex and multifactorial. Obesity is the interaction of as much as the individual facets of physiological, psychological, societal and environmental factors that appear to be important in causing obesity (25, 26). The interplay between these factors affects how individuals respond to food on a conscious and subconscious level, which then govern **eating behaviour** in different situations. The following section reveals some of the potential causes of obesity in more detail.

1.1.2.1. Biological factors

The French philosopher Voltaire declared that *"Nothing would be more tiresome than eating and drinking if God had not made them a pleasure as well as a necessity"*. What Voltaire said is explained scientifically by the fact that food intake is controlled by two pathways that are strongly integrated with the regulation of energy intake: the homeostatic (maintaining energy balance) and non-homeostatic (reward-related consumption) pathways. The homeostatic pathway involves energy intake based on signalling from fat stores (via the leptin hormone) and the gut (via the presence or absence of nutrients in the gut which signal the brain through gut hormones such as **GLP-1**). These adipose and gut hormones integrate with other neural signals that also come from the gut, particularly via the vagus nerve, to signal the brain stem, the hypothalamus and hindbrain circuitry to regulate our appetite (27). The non-homeostatic mechanisms of eating include learning, memory and cognitive processes that can affect feeding based on previously learned experiences and reward aspects of food. The homeostatic and non-homeostatic drivers for eating are linked. For example, GLP-1 is one of the endocrine signals that acts in various brain regions that are involved in both homeostatic and non-homeostatic

aspects of eating control. It acts via the vagal-brainstem-hypothalamic pathway to enhance gastric satiation signalling and suppresses food intake (homeostatic aspect) and via appetite- and reward-related brain regions, specifically the insula, amygdala, putamen, and orbitofrontal cortex (28) to reduce motivated responding for palatable food (non-homeostatic aspects) (29-31). The non-homeostatic pathway is thought to be more relevant to the excessive food intake seen in countries with high obesity rates. While cognitive and reward factors are thought to override the inhibitory mechanisms that regulate caloric intake (27). However, little is known about exactly how these non-homeostatic pathways in the brain influence food intake. Some regions of the brain have been described as particularly important in the reward and emotional response to palatable food or food-related cues as well as habitual behaviour patterns and sensory information, including taste (29-31). These forebrain regions include the striatum, the nucleus accumbens, the amygdala, the anterior insula, the orbitofrontal cortex and the anterior cingulate cortex (32). Functionally; 1- the striatum encodes motivational and incentive properties of food including decision-making, and reinforcement, reward perception (33-35), 2- the nucleus accumbens links motivation to action including processing the rewarding and reinforcing stimuli (36, 37), 3- the amygdala is involved in the sense of smell, emotional learning (38), and food palatability (39), while linking the homeostatic and non-homeostatic interactions, 4- the anterior insula encodes sensory information of taste (40), integrated with sensory cues to form flavour and responds to food cues and gut hormones, 5- the orbitofrontal cortex is involved in the integration of sensory, reward and cognitive aspects of decision-making(41).

1.1.2.1.1. The effects of genetic factors on body weight

Strong evidence points to genetic factors as being accountable for between 46% and 75% of variations in body weight, making some individuals more susceptible to obesity than others (42, 43). In a large-scale meta-analysis of 140,000 individuals across 31 twin studies, heritability was estimated as representing 75% of all variations in body mass index (BMI) due to genetic variations. The remaining 25% was due to people's diverse lifestyles (44). Several heritability studies, including twin and familial studies, examined the extent to which genes contribute to the variation in susceptibility to obesity. Familial studies showed that BMI is highly correlated with parental obesity, but they did not distinguish between genetic and environmental factors (45, 46). Studying the BMI of twins or adopted children, including a Danish adoption study of 540 adult adoptees, established that genes contribute to differences in body weight within a given population, as BMI is strongly correlated with biological parents, and less with adoptive parents (47, 48). In the Danish study, the adoptees were chosen from a population of 3580 to study to investigate the contributions of genetic factors and the family environment on human body weight. They found that the familial resemblance of obesity is mainly due to genes, whereas the family environment alone has no apparent effect (47). There was a strong relationship between the bodyweight of the adoptees and the BMI of their biological parents, but not with their adoptive parents. More recently, in 2016, Silventoinen et al. analysed the genetic and environmental contribution of 87,782 twins from 45 cohorts to BMI variation using genetic structural equation modelling. They found that at 4 years of age, the fraction of BMI variance explained by additive genetic variables was low in both genders, before increasing at 19 years of age. This result emphasised the important role genetic factors play in variations of BMI in adolescence (49). However, monogenic disorders leading to obesity, such as leptin deficiency and melanocortin 4 receptor (**MC4R**), account for less than 5% of obesity, indicating that genetic impacts on obesity are mainly polygenic. Molecular

genetic studies show that more than 100 genes are implicated in weight variation and obesity (50). The primary mechanism controlling the effect of genetics on weight is thought to be eating behaviour (food intake and eating behaviour traits) and appetite-regulating mechanisms (51). To summarise, while a genetic basis for obesity exists, the current global obesity epidemic cannot be explained by genetic changes alone. One useful and insightful analogy that describes the relationship between genes and obesity was expressed by George Bray when he said: "*the genetic background loads the gun, but the environment pulls the trigger*" (52).

1.1.2.1.2. The effects of stress on body weight

A history of psychological stress may also play a role in developing and maintaining obesity (53-56). When an individual is exposed to chronic stress, such as health concerns, financial instability, interpersonal strife, the stress of belonging to a stigmatised community or mental disorder, their stress response mechanism is continually triggered, and that can affect physical metabolism and the tendency to gain weight (57-59). For instance, appetite-related hormones increase during stress, resulting in increased appetite, particularly for high fat and high sugar "comfort" foods as a mechanism to regulate and suppress stress (54). A recent cross-sectional study examined the impact of **COVID-19**-related stress on energy-dense food intake during the pandemic. The findings showed that negative emotions brought on by the pandemic were associated with the risk of increased intake of palatable foods (60). Stress can also affect the brain's reward system. The activity of the prefrontal cortex, which is implicated in planning complex cognitive behaviour such as decision making, increases in the stressed brain (54). This can result in increased food consumption and impaired capacity to stop eating, both of which add up to a potent formula for obesity. Stress also influences sleep patterns and impacts sleep quality, leading to an increase in cortisol levels. Cortisol is a hormone that causes fat storage, and several research studies show a relationship between high cortisol levels in sleep-deprived adults and weight gain (61). During exposure to stress and favourite food cues, people with

obesity showed activation in the reward regions of the brain (such as the striatum, insula, and thalamus)(62). Such activation will enhance caloric intake (63). Although stress may increase the risk of obesity, the condition itself is related to heightened stress responses, meaning that people with obesity are more likely to suffer from stress, anxiety, and depression (64-66).

1.1.2.2. Psychological factors

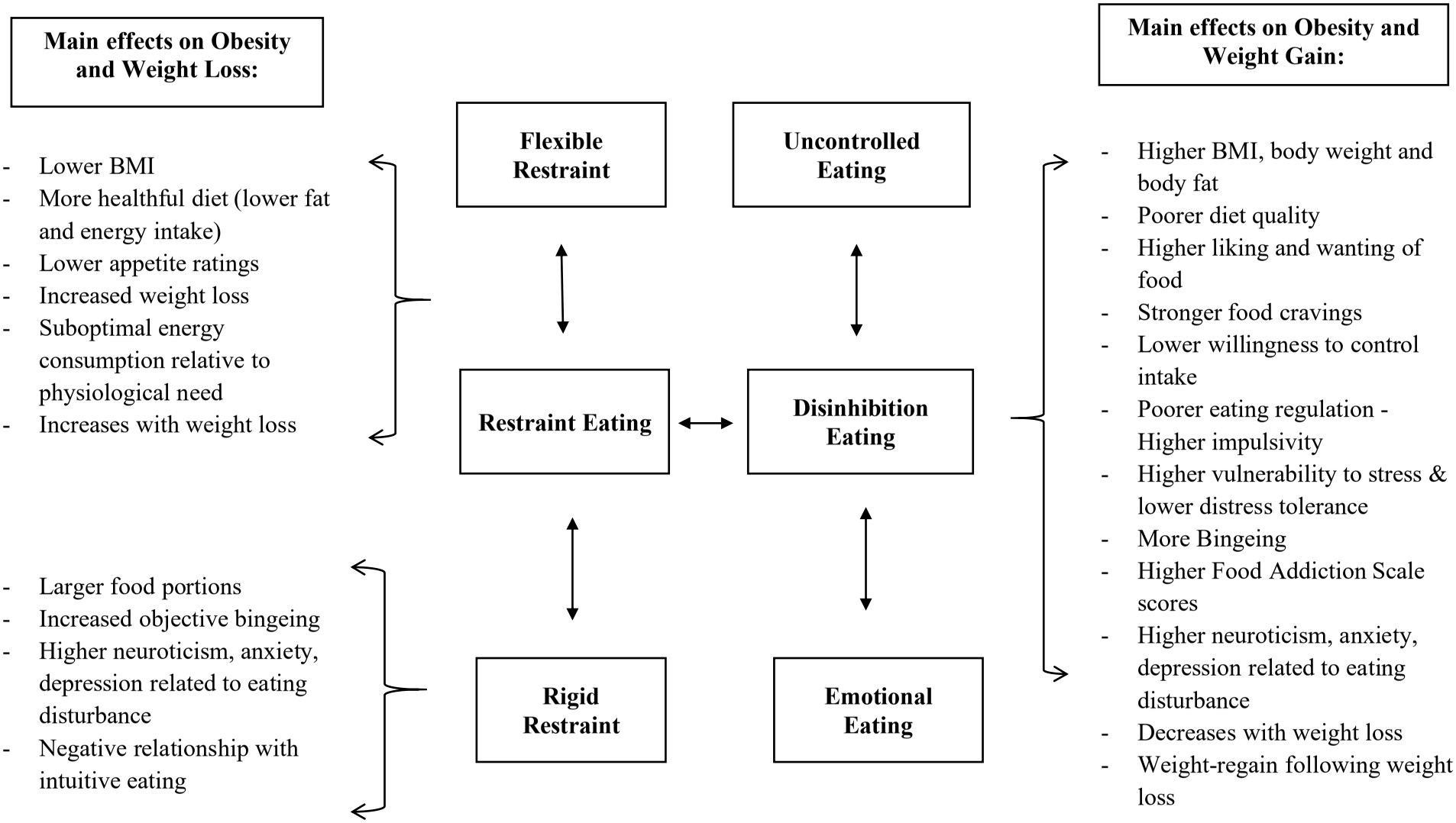
Food habits are highly subjected to several psychological traits and mental health problems. These are acquired through learned behaviour or inherited through genetic factors but are engaged in regulating brain reward sensitivity and food preferences. Their impact on controlling an individual's intake and eating behaviour may play a role in developing obesity. These factors include **dietary restraint**, **external eating**, **disinhibition**, and mental illnesses such as depression and anxiety.

1.1.2.2.1. Restraint and disinhibition eating

The relationship between dietary restraint and obesity is controversial. Restrained eating is described as a tendency to deliberately control food rather than relying on physiological signals (such as hunger and satiety) to control intake (67, 68). Several studies have shown that the rigid, all-or-nothing approach of dietary restraint can lead to overeating through emotional stress, and restrained dieters are at high risk of overeating and obesity (68). Meanwhile, flexible restraint is a more graduated approach in which fattening foods are permitted in limited quantities rather than avoided entirely. Questionnaires such as the Dutch Eating Behaviour Questionnaire (**DEBQ**) can be used to measure dietary restraint as well as emotional and external eating, and there are many different tools that can measure different types of dietary restraint (69, 70). In comparison to other questionnaires, the DEBQ is more internally consistent and reliable across subjects relating to varying weight and gender (71). In obesity management, rigid dietary restriction is often followed by disinhibition, or loss of control over

dietary consumption, resulting in overeating when a fast or a diet is broken or when emotional or external cues serve as triggers (72). Polivy and Herman (1985) argued that dieting caused binge eating and suggested that cognitive (rather than physiological) aspects of dieting – such as expectations and beliefs about foods – created this vulnerability (73). See Figure 1 on Page 24 for more details about the influence of restraint and disinhibition on obesity (74). Disinhibited eating relates to any stimulus (external or internal) that distracts dieters from their eating programme and leads to overconsumption and weight gain (68). Little is known about the underlying mechanisms that control these factors.

Figure 1: *Summary of the influence Restraint and Disinhibition have upon obesity*



1.1.2.2.2. Emotional and external eating

Emotional eating is positively associated with body weight (75). It more often describes eating in response to negative emotions such as anxiety and depression, as opposed to in response to internal hunger cues (76) but can also refer to eating more in response to positive emotions such as happiness and celebration. Emotional eaters tend to overeat and consume more fatty and sweet foods as a coping strategy in response to stress (68). Eating has the capability to reduce negative emotions and improve mood. Food elicits strong reward responses that enhance the emotional state, and the nutrients it provides can influence neurochemical and endocrine systems that are related to emotions. For example, fatty and sweet foods have been shown to increase opioid and serotonin neurotransmission in the brain, and therefore act as mood enhancers (77). A double-blinded study investigated the impact of intragastric infusion of a fatty acid solution on a behavioural measure (hunger, fullness, and mood using **VAS**) and neural level on the brain response to a sad emotional state (using **fMRI** to examine responses across regions of interest including the striatum, hypothalamus putamen, cerebellum, and right hippocampus). The participants received the intragastric infusing of fatty acid solution (2.5 g lauric acid) or saline whilst in the fMRI scanner and a sad emotional state was induced through sad music and pictures of sad faces. The infusion of fatty acids reduced the activation of the brain to that sad state, suggesting that food may suppress brain responses to negative emotional states (78). This finding indicating the presence of an interplay among emotions, hunger, food intake, and meal-induced sensations in health, which may have important implications for a wide range of obesity. Further, hormones that govern appetite may also mediate these stress-related responses. For instance, there is evidence from an animal study conducted to monitor food-reward behaviour in mice after exposure to a model of prolonged psychosocial stress using a standard pre-clinical behavioural task. In that task, a test mouse is introduced into the home cage of a different aggressive mouse for a 5-minute physical for 10-day. Ghrelin levels

were then assessed one day after the task. The results showed an increase in ghrelin level and conditioned place preference for high-fat diets among stress- exposed compared with non-stress- exposed mice (control). This suggests that the hunger hormone (ghrelin) may mediate stress-induced food-reward behaviour in mice (79).

External eating refers to eating in response to external stimuli – including the sight, smell or taste of palatable food – as opposed to internal cues such as hunger. Like emotional eating, external eating is also thought to be associated with overeating and obesity, but links between external eating and obesity remain under-researched (72). However, an association has been confirmed in a few small-scale studies (80-82) and has also been linked to food cravings (83). There is also a correlation between an individual's weight and their responsiveness to external food or environmental-related cues (80). Moreover, some brain studies suggest that damage to the frontal lobe may increase external eating, leading to hyperphagia and obesity (84). The degree of sensitivity to internal or external food stimuli can have an important impact on food intake. For example, individuals who are less sensitive to internal feelings of satiety are at greater risk of obesity. Similarly, those who are more sensitive to external food stimuli are more likely to consume more food in response to the sight, sound, smell or taste of certain foods – more likely high-calorie food. Furthermore, environmental triggers such as increased availability, convenience, the advertising of highly palatable energy-dense foods or larger portion sizes can lead individuals who are highly responsive to food cues and less sensitive to internal feelings of fullness to consume excess quantities. The degree of craving for high sugar or high-fat food is positively correlated with higher body weight (83). Overeating and access to palatable foods eventually lead to obesity, while palatable and energy-dense food, such as processed food, can overcome the innate sensory-specific satiety mechanism, leading to overeating during a meal (85). There are also cross-correlations and interactions between dietary restraint, external eating, disinhibition and emotional eating, however basic

mechanisms underlying such patterns show complex interactions which are poorly understood. However, they communicate with one another within the consciousness of the individual, resulting in additive or synergistic effects that show an association with obesity. This issue will be discussed in more detail in the following chapters.

1.1.2.2.3. Mental health problems

The scientific understanding of the association between obesity and psychological wellbeing is still limited, but the association appears to be bidirectional (86, 87). Poor mental health can be considered a risk factor for weight gain and has been found to increase the risk of obesity several-fold. Meanwhile, the risk of mental health issues in individuals with obesity – particularly mood disorders, anxiety, low self-esteem, and depression – has been documented to range between 30% and 70% (88-90). Although the mechanisms that link obesity with mental health are unclear, there are common pathophysiological pathways involved in the association, for instance, sedentary lifestyle, childhood trauma, and inflammatory changes (91). Furthermore, some antipsychotic and antidepressant medications can lead to increased appetite, weight gain and metabolic changes as potential side effects. (91, 92).

1.1.2.3. Environmental factors

Hippocrates was the first to argue that human health is influenced by environmental factors, nutrition, and lifestyle. Environmental factors such as the availability of highly palatable energy-dense foods, greater convenience, affordability and fast rates of consumption drive food intake (93) leading to what has been termed an "**obesogenic**" environment. Further factors contributing to overconsumption are the increases in portion size that have been observed across different foods and beverages (94, 95). There is also some evidence that the rate of eating affects energy intake and may be a contributing factor to weight gain and obesity. In a systematic review and meta-analysis of approximately 900 participants, a study of twenty-

two experiments was conducted to compare slower eating rates against rapid eating rates. Evidence showed that slow eating rates are associated with lower food intake compared to rapid consumption whereas no relation was found between eating rates and hunger following the meal, or up to 3.5 hours later (96). One possible explanation is that eating at a moderate pace elicits higher concentrations of anorexigenic gut peptides and favours earlier satiety and a lower caloric intake in comparison to eating quickly (97). Further, diverse epidemiological data looked at the rapid increase in obesity in Britain indicate that modern inactive lifestyles are at least as important as diet in the aetiology of obesity, and may represent the dominant factor in the modern obesity epidemic (98). In a review that explores the role of physical activity in obesity, findings indicate that people are adopting increasingly sedentary lifestyles in which physical work is replaced by automated and mechanised lifestyles, energy-saving domestic appliances and other inactive pastimes (99). The need to expend energy for thermoregulation is also minimised with central heating, and the overall result is often lethargy (98).

1.1.3. Type 2 diabetes

Obesity leads to a seven-fold risk of T2DM compared to people of normal-weight, with a threefold increase in risk for overweight individuals (101). Type 2 Diabetes (T2DM) can lead to substantial health complications including kidney failure, cardiovascular disease, and the risk of amputations all of which have adverse effects on quality of life and increase healthcare costs. The global prevalence of type 2 diabetes is predicted to reach 693 million by 2045 (100). In 2017, the prevalence of deaths attributable to diabetes was approximately 5 million in individuals aged between 20–99 years. The financial burden of type 2 diabetes was estimated in 2017 to be $850 billion across the world (100). Increases in adiposity induce insulin resistance and compensatory increase in insulin secretion from the pancreatic β-cells, eventually leading to β-cell dysfunction and further accumulation of fat tissue. There is no

question that weight loss is one of the main drivers of improved insulin sensitivity, especially in the early stages of T2DM, due to improvements in insulin sensitivity in the liver, adipose tissue and muscle, as well as the recovery of β-cell function (102, 103). As diabetes is a chronic disease, long-term weight loss is needed to maintain the improvement in insulin sensitivity.

1.1.4. Currently available treatments for obesity

Lifestyle modification, pharmacotherapy and bariatric surgery are the obesity treatment approaches supported by the most robust empirical evidence (104, 105). The following section will briefly discuss these different approaches.

1.1.4.1. Lifestyle and weight management modification

Lifestyle modification (including behavioural-based instructed modification, caloric restriction and increased physical activity) is considered the first line of weight management and is recommended by The National Institute for Health and Care Excellence (**NICE**) for the treatment, prevention and management of obesity and T2DM (106). In a meta-analysis conducted to evaluate the effects of lifestyle change on clinical markers known to be associated with the development of cardiovascular diseases, Chen et al. (2015) found that lifestyle interventions resulted in significant metabolic benefit in patients with T2DM, including reduced BMI and blood pressure and improved haemoglobin (HbA1c) levels (107). In a more recent study, (I-SatPro study) a multifaceted approach to weight loss for patients with obesity achieved significant weight loss (-13%) sustained up to a year after 30 weeks of intervention (-14%). The approach encompassed dietary modification (without calorie restriction or replacements), with time-restricted eating, physical activity and coaching to support behavioural change for 84 participants, who attended fortnightly group sessions. Interestingly, the I-SatPro intervention (as opposed to calorie restriction) did not show a reduction in weight-adjusted resting energy expenditure (**REE**) measured by indirect calorimetry, although it did

show a reduction in feelings of hunger measured by the Three-Factor Eating Questionnaire. I-SatPro intervention showed improvements in HbA1c (pre-diabetes and T2DM, N=16), blood pressure and health-related quality of life (6). However, it should be noted that the I-SatPro Intervention was not part of a randomised controlled trial. Although it is possible to achieve significant weight loss through lifestyle intervention, this requires an intensive approach including regular physical activity and continuous support (108) and long term weight loss is mostly not sustained (109).

1.1.4.1.1. Calorie restriction and very low-calorie diets

Calorie restriction is an effective short-term way of losing weight, and there are several diets currently available. A full explanation of all calorie-restrictive diets falls outside the remit of this theses, but a Low-Calorie diet is defined as a diet plan that involves eating between 800 and 1,500 calories a day and a Very Low-Calorie Diet as a diet plan that involves eating 800 calories a day. Low-Calorie (LCD) and Very Low-Calorie Diets (VLCDs) can drive considerable weight loss of between 10 to 25% over 3-4 months (110, 111) with improvements in blood glucose level and cardiovascular risk factors (112). In the largest and longest lifestyle weight-loss intervention combining physical activity and dietary programme, the Look-AHEAD trial reported a calorie-restricted (VLCD) weight loss of ≥ 5% that was sustained up to eight years in 50% of patients, with a significant improvement in other obesity-related comorbidities such as hypertension and renal disease (113). In a real-world clinical setting, the **DiRECT** study was the first to show that diet can induce remission of diabetes in over 45% of people, who lost an average of 11% of their body weight which is sustained for 2 years. Patients were advised to follow a total diet replacement procedure of about 800 kcal/day for 12-20 weeks, then follow a food reintroduction stage for 2-8 weeks, followed by a period of structured support for weight-loss maintenance (114, 115). However, weight loss achieved through

calorie restriction is usually regained between 1-2 years and beneficial long-term weight loss is usually only maintained in about 20% of the population (116, 117). Several deterrent factors working together may prevent the long-term success of low-calorie diets in diet-induced weight loss. The available clinical data, for example, shows that diet-induced energy deficits run counter to human physiology, causing the body's hormones to initiate a counter-response to oppose the maintenance of a bodyweight that is different from the usual weight (118, 119) by decreasing circulating satiety hormones and exacerbating hormonal hunger response hormones (Ghrelin), thus increasing hunger and reducing satiety (120-122). This may explain the increased feelings of hunger during dieting among participants with obesity, which may prevent them from adhering to **a low-calorie diet**. A decrease in REE is also seen when following a low-calorie diet – a decrease that remains even after the weight has been regained (118).

The physiological responses to starvation or low-calorie dieting affect the long-term adherence to a VLCD. Starvation lowers **PYY** levels and raises levels of ghrelin due to the loss of fatty tissue in the body, producing feelings of reduced satiety and increased hunger, meaning that patients are likely to increase their consumption rates (119, 123). These findings have been corroborated by using functional MRI (fMRI) tests. Losing weight by restricting calorific intake has been found to be associated with an increase in brain activity in areas concerned with reward and pre-occupation with food, as demonstrated when participants on a reduced calorie-diet, were compared to a post-bariatric cohort in an fMRI study. Both groups were shown visual food cues of different foodstuffs, which acted against further weight loss (124). The calorie-restricted diet group also showed lower levels of self-esteem, lower motivation levels, lack of time, mood swings, and non-adherence due to the lack of any network that included psychological support. Such factors were all considered to be barriers preventing long-term lifestyle modifications or weight loss and causing failure to maintain any weight that

was lost in calorie-controlled dieting patients. Therefore, a major shift in dietary advice may be needed to develop more sustainable weight loss strategies. We can infer from these studies that lifestyle interventions with calorie restriction as a treatment for obesity and T2DM can work in selected patients, but for the majority, such approaches will not work alone and should be supported by other factors, such as pharmacotherapy.

1.1.4.2. Pharmacotherapy for obesity

Weight-loss intervention demands a comprehensive and multimodal approach that makes the best use of lifestyle and behavioural interventions. Pharmacological therapy can then be used to help patients with obesity who fail to respond to lifestyle modifications alone. When intensive behavioural therapy is administered alongside other weight-loss approaches, an increase in the percentage of weight loss was observed (125). However, despite the magnitude of the problem, current pharmacotherapy is limited. Five major anti-obesity medications that are available and approved by Food and Drug Administration (**FDA**): phentermine, orlistat, phentermine/topiramate, naltrexone/bupropion and Liraglutide (Liraglutide 3mg/Saxenda® 2.4 mg) which is the only injectable formulation (126). In Europe, only orlistat (marketed as Xenical®) and Liraglutide have been approved by the European Medicines Agency (**EMA**) for treating obesity. Sibutramine, Rimonabant, and more recently Lorcaserin have been withdrawn from the market due to unacceptable side effects (127) (Table 1 on Page 34). The FDA and the EMA use different criteria when assessing the suitability and safety of any new anti-obesity drug. However, for both agencies, a placebo-subtracted weight loss of at least 5% needs to be shown, with a favourable benefit-risk profile, before the drug can be considered for clinical use (128). Orlistat has shown improvement in glycaemic parameters (129), but it can lead to a deficiency of fat-soluble vitamins as it decreases fat absorption by up to 30% (130). Liraglutide (131) has a noticeable effect on reducing diabetes and works as a satiety signal. In 2015, the EMA approved it as a drug for obesity, offering a sustained weight reduction over three years

period (-6%) as shown in the SCALE Obesity and Prediabetes trial (132). The SCALE Obesity and Prediabetes trial was a series of four randomised, double-blind, placebo-controlled studies with more than 5000 participants to investigate the efficacy and safety of liraglutide 3.0 mg for weight management (133-136). More recently, Semaglutide Treatment Effect in People with obesity (STEP) program was conducted among 1961 adults to investigate the effect of Semaglutide (2.4 mg once weekly) on weight loss compared with placebo across five phases 3 trials (137). The result showed that participants who received Semaglutide were more likely to lose 5% or more than those who received a placebo (86% vs 31.5% respectively) (138). However, concerns have since been raised regarding increased risks of pancreatitis and medullary thyroid cancer (relatively rare) related to the long-term use of Liraglutide. Most of these anti-obesity drugs have an efficacy of 3–7% (estimated net weight loss) in clinical trials, but individual variations in response rates mean that the future direction for pharmacotherapy research in obesity might include the potential for personalized medicine to target early responders to anti-obesity drugs. In general, the weight loss from medication is modest – at best 10% – which is considered an inadequate reduction when treating **class-3 obesity** patients (severe obesity with a BMI over 40). Moreover, the cost of prescribing some medications becomes prohibitive over an extended period and the delivery method of subcutaneous injection is not acceptable to all patients.

Table 1: *Past and current anti-obesity drugs*

Ref.	**Components (**Drug**)**	**Approved by**	**Mechanism**	**Weight-loss Effectiveness**	**Side effects**
			Current Anti-Obesity Drugs		
(139)	**Phentermine** (Lonamin®)	FDA in 1959	- Appetite-suppressing	13 kg	- Increase in HR and/or BP, dizziness, dry mouth, constipation, insomnia
(126, 140, 141)	**Orlistat** (Xenical®, Alli®)	FDA & EMA since 1990	- Lipase inhibitor	3–6kg	- Flatulence - Steatorrhea - Abdominal pain - Malabsorption of fat-soluble vitamins
(142-145)	**Phentermine/Topiramate** (Qsymia®)	FDA in 2012	- Unknown - Amine mimetic	7–11kg	- Cleft palate (baby) - Loss of concentration - Numerous **CNS**
(125, 146, 147)	**Naltrexone/Bupropion** (Contrave®)	FDA in 2014	- Opioid Antagonists - Amine uptake inhibitor	5–9 kg	- Nausea and headache - CNS/CVS
(132, 148, 149)	**Liraglutide** (2.4mg Semaglutide / 3mg Saxenda®)	FDA in 2014 EMA in 2015	GLP-1 agonist - Suppress appetite and food intake	3–7kg	- Nausea, vomiting, abdominal pain, and diarrhoea
			Past Anti-Obesity Drugs		
(127, 150, 151)	**Sibutramine** (Meridia®)	FDA & EMA - In 1997 - Withdrawn in 2010	- Enhancement of satiety: (+) **POMC**/CART (-) **NPY**/AgRP neurones - Inhibiting the fall in BMR - Promoting thermogenesis	7–8kg	- Increased risk of cardiovascular disease and death
(152-154)	**Rimonabant** (Acomplia®, Zimulti®)	EMA in 2006 - Withdrawn in 2008	- A centrally acting cannabinoid 1 receptor antagonist - Influencing the brain reward system	3–6.6kg	- Risks of psychological adverse events
(155-158)	**Lorcaserin** (Belviq®)	FDA in 2012 - Withdrawn in 2020	- Selective 5-HT2c agonist - Promote satiety - Decrease food intake in CNS	5.8– 6kg	- CNS - Cardiac - Possible risk of cancer

Abbreviations: FDA, Food and Drug Administration; EMA, European Medicines Agency; CVS, Cardiovascular System; CNS, Central Nervous System; 5-HT, 5-hydroxytryptamine; Ref., References.

1.1.4.3. Bariatric surgery

Bariatric surgery is the most effective long-term treatment for severe obesity and T2DM. It is a comprehensive term for different types of procedures that involve a manipulation of gastrointestinal anatomy. The concept of bariatric surgery emerged during the 1950s when significant weight loss was observed in patients that had partial gastrectomy or small intestine resections (159-161). This inspired the development of different procedures to promote weight loss through either mechanically restrictive procedures, malabsorption or combined malabsorptive and restrictive procedures. Since then, further modifications have led to the development of current bariatric procedures including Laparoscopic Gastric Banding (LGB), Sleeve Gastrectomy (SG), and Roux-en-Y Gastric Bypass (**RYGB**). In order to qualify for bariatric surgery, patients should have a BMI equal to or greater than 40 kg/m^2 (37.5 kg/m^2 in Asia) or have a BMI of between 35 and 40 and at least one major obesity-related co-morbidity, such as T2DM (162). More recently, the American Diabetes Association has expanded eligibility criteria to include adults with T2DM and BMIs of 35.0-39.9 kg/m^2 who have not achieved sustainable weight loss and improvement in comorbidities (including hyperglycaemia) using reasonable nonsurgical methods (163).

1.1.4.3.1. Laparoscopic Adjustable Gastric Banding (LAGB)

LAGB was designed as a restrictive procedure that represents the least invasive form of bariatric surgery. The procedure involves placing a saline-filled silicone band, with an adjustable balloon below the gastro-oesophageal junction. This creates a new gastric pouch in the size of a thumb, restricting the amount of food that can be eaten (164). The size of the pouch can be adjusted through an injection port under the skin into which saline is injected (Figure 2.B on Page 37). However, banding is associated with complications such as port infections, band slippage, ulceration, pouch dilation and the need for further operating

procedures. Long-term follow-up revealed that complication rates increased over time and a high percentage of patients had to have additional operations (165).

1.1.4.3.2. Vertical Sleeve Gastrectomy (VSG)

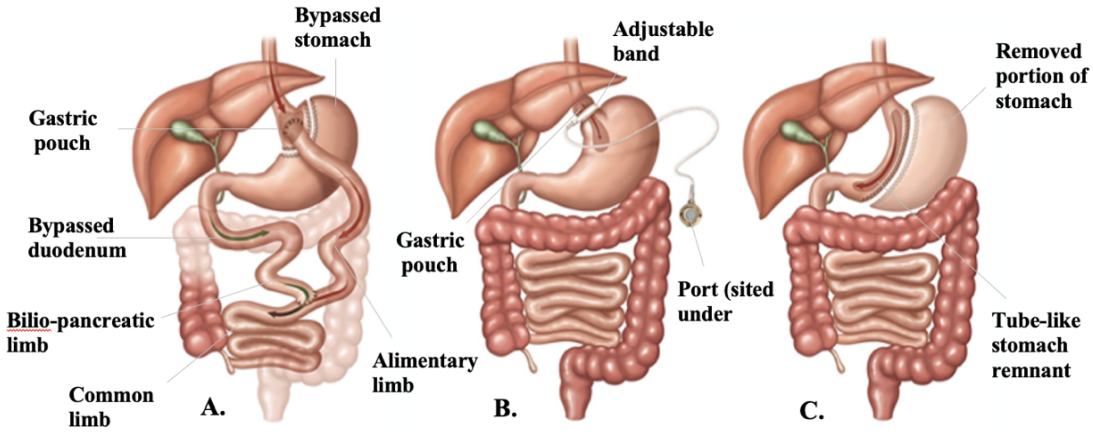
Worldwide, **VSG** is the most performed of the irreversible procedures that are performed laparoscopically (45.9%) followed by RYGB (39.6%) (166, 167). The procedure involves the resection of most of the stomach along the greater curvature, leaving a narrow tube-shaped structure referred to as a sleeve (Figure 2.C on Page 37). This results in reduced calorie intake and weight loss as well as improvements in obesity-related comorbidities. It has been suggested that a combination of biological and neurobehavioral effects are involved in the mechanism by which VSG induces weight loss (168). However, complications such as gastric leakage and nutritional deficiencies may occur, although the latter tend to be milder than those seen after RYGB (169).

1.1.4.3.3. Roux-en-Y Gastric Bypass (RYGB).

The RYGB procedure involves a partial gastrectomy and the creation of a small upper gastric pouch with an estimated size of 15-25 ml which is then linked directly to the lower part of the small intestine (the mid-jejunum) to create the Roux limb approximately 100–150 cm in length. The bypassed duodenum is attached to the distal jejunum, allowing bile and pancreatic juices to meet diverted food at a point lower down the gastrointestinal tract (the common channel) (170) (Figure 2.A on Page 37). Like the VSG, the RYGB procedure is performed laparoscopically, although technically speaking it is reversible. As far as the long-term effects of bariatric surgery are concerned, the weight loss and reduction in co-morbidities after RYGB are better than that of VSG (171), although long-term complications may include vitamin and trace element deficiencies, osteoporosis and post-prandial hypoglycaemia. The latter is relatively rare. Additionally, RYGB patients need life-long multi-vitamin replacement and

follow-up (172). For the purposes of this thesis, the discussion will focus on RYGB and an understanding of the physiology that underpins gastric bypass success.

Figure 2: *Anatomy of the 3 most common bariatric procedures*



A. the Roux-en- Y gastric bypass (RYGB); **B.** the Laparoscopic adjustable gastric banding (LAGB); **C**. the Sleeve gastrectomy (SG)

Figures are adapted from Al-Najim et al. (2018) (173)

1.1.4.4. Bariatric surgery and weight loss

Bariatric surgery leads to sustained weight loss. The results of the long-term effects of bariatric surgery from the Swedish Obese Subjects (**SOS**) study showed that RYGB provides better levels of weight loss than lifestyle management and in comparison to the other bariatric procedures at 15 years (RYGB 27%, VBG 18% and banding 13%) (109). Moreover, the mortality rate is also reduced by 23.7% in the surgical group compared to control groups (174). Several well-established RCTs involving bariatric procedures and intensive lifestyle management have confirmed the above findings. Five years after RYGB surgery, patients had maintained weight losses of between 23 and 28%, a figure that was much higher than any result achieved on lifestyle interventions (4 – 6.9%) or sleeve gastrectomy (19%) (168, 175). RYGB-associated weight loss far exceeded losses following drug interventions or calorie-controlled diets and was accompanied by an improvement in factors associated with cardiovascular risk (176).

1.1.4.5. Bariatric surgery and type 2 diabetes

Bariatric surgery, particularly RYGB, has profound and substantial effects on glycaemic control in most patients with T2DM. In 1995, Walter Pories was the first surgeon to report the rapid and profound effect of RYGB on glucose levels in patients with T2DM within a few days postoperatively (177). Since that time, RYGB surgery continues to offer research avenues towards the understanding of diabetes. A meta-analysis of more than 100 studies clearly showed that bariatric surgery can resolve or improve T2DM in 80% of patients with obesity following RYGB surgery (178). However, the majority of studies included were retrospective in nature. More recently, In the SOS study, patients who underwent RYGB procedures showed remission rates of diabetes that were sustained in 36% of the cohort for up to 10 years (109). The diabetes remission rate in the SOS study was defined as fasting glucose of <7 mmol/L.

Further RCT studies confirmed these findings using stricter criteria to define remission, as opposed to the remission rate following intensive medical and lifestyle intervention, which was generally poor (168, 175, 179-181). Participants with T2DM managed to come off all glucose-lowering medications after RYGB compared to medical intervention for up to 2 years, a process that was sustained 5 years after surgery (168, 175) As well as long-term outcomes on diabetes for RYGB patients, many other physiological and behavioural aspects are altered following RYGB, including the levels of circulating **anorexigenic gut hormones** as well as food preferences and eating behaviour, which may be linked to changes in taste detection and reward. However, Lean et al. (2019) in their DiRECT trial reported that more than a third of patients who showed T2DM remission at one-year following substantial weight loss through VLCD, sustained this remission after two years (remission defined as HbA1c of less than 48mmol/mol) (115). Sustained remission was linked to sustained weight loss. Moreover, a more recent study by Yoshino et al. (2020) published in the *New England Journal of Medicine* reported that patients who had lost weight by dieting had undergone similar improvement in glycaemia and insulin sensitivity to those in patients who had lost the same amount of weight following RYGB surgery (103). These studies showed promising results for individuals living with obesity and T2DM, but only about 20% of the population are generally able to maintain their weight loss for up to 1-2 years through non-surgical interventions (116, 117). Understanding the mechanisms that enable RYGB patients to sustain long-term weight loss should include all the metabolic benefits that could accelerate the production of a novel, and potentially safer, obesity and T2DM medications.

1.1.4.6. Mechanisms mediating weight loss in RYGB

Several mechanisms have been put forward to explain the mediators of favourable change post-RYGB that can contribute to long-term weight loss. The following section will focus on some of these mechanisms.

1.1.4.6.1. Evidence for gastric and calorie restriction

When the RYGB was first used, it was thought to function purely through mechanical restriction. However, this idea has been discounted by the evidence. Human and animal studies of patients who underwent RYGB surgery reported a reduction in their calorie intake and meal size but lacked the expected increase in the frequency of eating that would occur if reductions in food intake had been purely due to restrictions in volume (182-184). In addition, non-surgical dietary restriction approaches typically deliver inferior weight loss in comparison to RYGB (185). Therefore, if restriction does play a role in weight loss following RYGB, it appears to be a minor one.

1.1.4.6.2. Evidence for gut hormones

As well as playing a role in digestion, the gastrointestinal tract regulates the signalling pathways between the gut and the appetite centres in the brain by releasing hormones in response to the sensing of nutrients as part of the **gut-brain axis**. Previous research has shown that gut hormones can induce feelings of satiety, enhancing insulin release and delaying food absorption**.** Alterations in these hormones after RYGB provide strong evidence to explain the mechanisms by which surgery reduces appetite and induces sustained weight loss. Anorexigenic hormones are secreted from L cells throughout the GI tract, which respond to food intake to promote the effect of satiety (186). Glucagon-Like Peptide-1 (GLP-1), Oxyntomodulin (**OXM**) and Peptide YY_{3-36} (PYY_{3-36}) are examples of anorexigenic gut hormones that have been found to be elevated at least threefold postprandially after RYGB (187-191). A single infusion of these anorexigenic hormones (GLP-1 (192), or OXM (193), PYY_{3-36} (194, 195) has been shown to suppress appetite and reduce food intake in normal-weight people and participants with obesity. Moreover, the subcutaneous co-infusion of GLP-1 and PYY_{3-36} has been shown to reduce food intake and reduce the activity of the brain's reward region in response to visual food stimuli, as demonstrated during an fMRI study (196).

When GLP-1 and PYY_{3-36} were combined with OXM, a further 32% reduction in food intake was observed in participants with obesity compared to the placebo (197). Meanwhile, reversing PYY_{3-36} and GLP1 responses with octreotide (a somatostatin analogue) reduces satiety and increases food-related fMRI activation in RYGB patients (189). This increase in satiety is not seen following the equivalent weight loss through other dietary or lifestyle modifications (187) or through gastric banding, where changes in gut hormones are not observed (109, 177). This makes studying gut hormones a promising approach to treating obesity, and also means that it may be possible to treat obesity by mimicking post-operative effects by infusing gut hormones.

1.1.4.6.2.1. *Glucagon-Like Peptide-1 (GLP-1)*

GLP-1 is a peptide hormone secreted from enteroendocrine L-cells located in the small intestine (the distal jejunum and ileum), and from a discrete population of hindbrain neurons in the brainstem on the consumption of food (198, 199). L-cells are stimulated by bile acids and by exposure to nutrients – mainly glucose, although lipids and proteins have also been shown to trigger GLP-1 release (200, 201). GLP-1 works through the activation of GLP-1 receptors (**GLP-1R**) on ß-cells that activate the protein kinase A and exchange proteins activated by cAMP2 that stimulate insulin secretion (202). It is also triggered by the activation of GLP-1R in the nucleus of the solitary tract (NTS) in the paraventricular nucleus of the hypothalamus in the brain to suppress food intake. The activation of GLP-1R appears to act as a satiety signal hormone that delays gastric emptying, enhances ß-cell proliferation, stimulates the vagus nerve and suppresses appetite and glucagon secretion (200, 203), thereby reducing food intake (192). GLP-1 may also play a role in taste preferences (204). The post-prandial secretion of GLP-1 is found to be low in individuals with obesity (200), and while it is unchanged by dieting (187), levels increase within weeks of RYGB (200, 205-208). Fasting levels of GLP-1 are usually low, but it is released rapidly within 10-15 minutes of eating, Levels peak at around 30 minutes. GLP-1 has a short half-life of 1-2 minutes and is broken

down by Dipeptidyl Peptidase 4 (**DPP-4**) and neural endopeptidase to an inactive form (9-36) (209). Liraglutide (2.4 mg Semaglutide/ 3mg Saxenda) is the only FDA (2014) and EMA (2015) licenced GLP-1R agonist for obesity. It acts as an adjunct to a reduced-calorie diet and is found to contribute to improved health-related quality of life (132, 148, 149, 210).

1.1.4.6.2.2. Oxyntomodulin (OXM)

OXM is a peptide hormone (a 37-amino acid peptide) co-released from the L cell alongside GLP-1 following nutrient ingestion. Its level peaks around 30 minutes after a meal (211). Like GLP-1, OXM mediates anorectic effects through GLP-1R activation and is believed to work through the GLP-1R as well as the Glucagon receptor (**GCGR**) and the hypothalamus through hitherto unidentified receptors (212). No native OXM receptor has been identified as yet, but OXM binds to existing receptors with less affinity than native ligands (213). OXM has been shown to reduce energy intake and delay gastric emptying and glucose-dependent insulin secretion (212). The peripheral infusion and chronic subcutaneous injection of OXM induce weight loss by inhibiting food intake in rats (214) as well as in normal-weight humans (193) and participants with obesity (215). Cohen et al. (2003) suggested that reductions in appetite that may be associated with disorders of the gastrointestinal tract could be caused by elevated levels of OXM (193). OXM also increases activity-related energy expenditure (215). OXM levels in individuals with obesity and after dieting are unknown, but postprandial levels of OXM post-RYGB have been found to increase (212). Recent results from our lab have demonstrated for the first time that a combined subcutaneous infusion of the three gut hormones GLP-1, PYY_{3-36} and OXM (**GOP**) was highly effective in reducing food intake by a mean of 32% in participants with obesity compared to placebo (197).

1.1.4.6.2.3. Peptide YY3-36 (PYY_{3-36})

PYY (a 36-amino-acid peptide) is excreted from the L-cells, the pancreas and brainstem neurons after eating, particularly after consuming fats and proteins, in proportion to the caloric content of a meal. PYY_{3-36} acts through Y2 receptors (GPCR) throughout the central nervous system and the vagus nerve (200). It is normally released within 15 minutes after a meal, and levels tend to peak 1-2 hours later (216). Like GLP-1, PYY_{3-36} reduces appetite and energy intake, delays gastric emptying, promotes insulin secretion and stimulates the vagus nerve (196, 200). Feelings of anorexia are caused by PYY_{3-36} through the activation of Y2 receptors on presynaptic hypothalamic **NPY**/**AGRP** neurons, leading to the inactivation of these neurons. The postprandial level of PYY_{3-36} in individuals with obesity is found to be low (200). Evidence for PYY_{3-36} levels in diet-induced weight loss suggests that PYY decreases after dieting (119, 217). A PYY_{3-36} infusion is found to reduce food intake in individuals with obesity (195) and reduce weight after long-term infusion in rodents (194). The reduction in rising basal and postprandial PYY_{3-36} levels in individuals with obesity compared to people of normal-weight suggests that the hormone is involved in the pathogenesis of obesity (195). The same group of researchers reported a 30-31% decrease in food intake after PYY_{3-36} infusion in individuals with obesity and lean subjects respectively, as well as a reduction in plasma levels of the ghrelin hormone that regulates hunger. Svane et al. (2016) showed an increase in food intake of 20% after RYGB surgery when both GLP-1 and PYY_{3-36} were blocked with Exendin 9-39 and a Dipeptidyl peptidase-4 inhibitor respectively. This result supports the idea that these hormones decrease levels of eating postoperatively (218).

1.1.4.6.3. Evidence of satiety

Patients who underwent RYGB reported decreased hunger and increased satiety, resulting in decreased caloric intake (189, 191). This reduction in food intake was found to be sustained for at least 2 years postoperatively (219). The elevation in anorectic gut hormones GLP-1, OXM and PYY, and the reductions in the orexigenic hormone (Ghrelin) that are reported post-surgery are found to promote these changes in feelings of satiety (123). A single, dual or triple infusion of GLP-1, OXM or PYY has consistently resulted in a reduction in calorie intake and enhanced satiety in normal-weight people and individuals with obesity (192-195). However, blocking the action of these anorectic gut hormones with Octreotide resulted in reduced satiety and increased food intake in post-RYGB participants (189). All these changes in physiology suggested that these gut hormones represent an essential contribution and a supportive factor to the substantial and sustained weight loss observed following RYGB surgery. In further support of their role on satiety, De Silva et al. (2011) demonstrated that co-infusions of GLP-1 and PYY during an fMRI study resulted in reduced Blood Oxygen Level Dependent (BOLD) activation compared to saline, in a pattern similar to a state of satiety in normal-weight participants. A decrease in food intake followed, compared to saline during an ad libitum meal, which was comparable to the fed state (196).

1.1.4.6.4. Evidence for changes in food preference

Food preferences and eating behaviour have been implicated in the pathogenesis of obesity. Behaviour modification and dietary control, therefore, remain a cornerstone of obesity treatment. Meanwhile, alterations in eating behaviour and food preferences have been reported after RYGB (220). Following RYGB, patients were found to adopt healthier eating behaviour (221) and tended to prefer low-fat and low-sugar food compared to pre-operatively. The increase in post-RYGB satiety may also affect underlying changes in food preferences and eating behaviour after RYGB, as behaviour is influenced by hunger and the reward value of

food (222). Functional MRI studies have shown that the appeal of high-calorie food pictures is reduced after RYGB surgery, and that this reduction cannot be explained by differences in hunger levels (223). This could potentially explain the favourable effect of RYGB on long-term weight loss. Halmi et al. (1981) were the first to report a change in macronutrient composition following RYGB, when patients reported they consumed fewer calorically dense and carbohydrate-rich foods (182). Halmi's group findings encouraged other researchers to explore the effect of bariatric surgery on food preferences and macronutrient consumption. Several other short-term studies confirmed Halmi's results (224-229). A more recent two-year follow-up study by Coluzzi et al. (230) examined changes in food intake that were connected with changes in taste, once again using verbal reporting. Six months after the surgery, the daily calorie consumption of participants had fallen by an average of 68% – a reduction that was maintained for two years. Meanwhile, 75% of participants reported taste changes associated with a lack of interest in sweets, high-fat food or alcoholic drinks (230). In the longest prospective study, involving 80 participants, there was an increase in the percentage of protein intake, a reduction in fat and no change in carbohydrates observed eight years after RYGB compared to baseline measurements (228). Other studies reported changes in the macronutrient composition and total food intake following RYGB, although findings varied. In general, lower intakes of fats and calories were observed (182, 224). At six years post-RYGB, Olbers et al found a lower contribution of fatty and sugary food towards total food intake, and a predominance of fruit and vegetables in the diets of post-RYGB patients compared to an LGB cohort (231). A similar study supported these findings, reporting a reduction in sweet and dairy consumption of 14-21%, while those who had a horizontal gastroplasty procedure showed no such changes compared to baseline levels (226). In an animal study, rodents that had RYGB procedures also avoided fatty and sweet food compared to a control group (183, 232).

The discrepancies between the studies discussed above are perhaps related to methodological differences in the practises used to collect data. Food diaries, questionnaires and interviews all have their disadvantages, as they are not objective and rely entirely on patients' reporting. Even though post-RYGB patients say they have an aversion to fried foods, sweets, and chocolate, researchers cannot be sure whether this reflects conscious avoidance, assumed expectations or advice and a sense of responsibility engendered by surgical intervention. Responses may reflect any or all these factors, or other yet unidentified responses to surgery.

1.1.4.6.5. Evidence for change in taste

1.1.4.6.5.1. Taste system

A multisensory process guides our food preferences, and this process includes sight, smell taste and touch. Taste is activated when a stimulus contacts epithelial receptors on the tongue, palate, upper oesophagus and throat (233). These receptors are located throughout the mouth in groups of 50 to 100 (234). Each taste receptor is designed to detect a specific kind of taste with neurons responding to the five basic tastes – sweet, salty, umami, sour and bitter. Sweet tastes are usually associated with carbohydrates, while saltier tastes reflect the presence of sodium. Bitterness identifies potential toxins; sour reacts to acids; umami relates to amino acids while savoury tastes are associated with meat. Sweet taste receptors occur in two forms, TIR2 and TIR3, and these are G-protein coupled receptors (CGPRs) (204). When the food is in the mouth, signals are sent to different parts of the body from the taste receptors to provide indications of quality, intensity, and pleasure. The gastrointestinal system responds by sending signals that reflect the nature of what is being tasted, deciding whether it is nutritious or toxic and reacting accordingly through ingestion or rejection (swallowing or spitting) (234). When sugars or artificial sweeteners activate taste buds, nerve impulses are triggered in the form of taste signals (204, 235), The sense of taste is controlled via a central pathway between the

Nucleus of the Solitary Tract (NTS), which is located within the brain stem and somatosensory cortex. Brain reward systems are activated in the secondary taste cortex, which includes the amygdala and the orbitofrontal cortex, and these reward systems activate the behavioural areas in the brain, the cingulate cortices and the striatum.

Liking and **wanting** are two separate reward valence factors that work independently and interdependently (236). Liking is a binary reaction, a yes/no response, and has no link to the food's nutritional value, but wanting is more complex, and must by necessity exist independently of enjoyment and be increased through hunger (237). Wanting food also involves memory, which indicates likes and dislikes based on historical sensory interactions (68). We may like something but not want or need it when full. This is known as devaluation, a feeling in which fullness temporarily reduces the values and sensory properties of food cues, although this might not relate to all types of food. Based on this process, liking can be considered as a conditioned preference, which depends on how often and for how long people are exposed to different tastes. Food consumption activates reward systems that enhance mood, encouraging repeat consumption. In the end we become used to enjoying certain types of food, and this conditions our personal preferences (68).

1.1.4.6.5.2. Taste changes after RYGB

Studies have proved that there is no difference in sweet taste **Detection Thresholds** between people with obesity and people of normal-weight (232, 238-242). However, many RYGB patients report changes in taste, including sweet aversion, following surgery. The literature is not conclusive about changes in sweet taste detection thresholds after bariatric surgery, and changes may be related to weight loss. Methodological inconsistencies and relatively small sample sizes limit the interpretation of existing studies, but it has been suggested that RYGB surgery leads to an increase in taste acuity, bringing a more intense perception of sweetness

that results in shifts in food preferences. As a result, people who have undergone RYGB may adjust their behaviour and reduce their intake of high-sugar food. The reduction in sweet detection threshold observed post-RYGB was assessed using increasing concentrations of sweet solutions separated with water, but no changes were observed after LGB or calorie-restricted diets (232, 243). Bueter et al. (2011) investigated changes in sucrose preferences after RYGB in humans and rats. They found that after surgery, **taste sensitivity** in terms of detecting lower sucrose concentrations in humans increased (232), which can be ascribed to changes in the **sensory, reward and physiological domains** of taste (244, 245). The **sensory domain** consists of two functions – the ability to detect stimuli and the perception of the intensity of suprathreshold concentrations of various taste solutions (*Is this drink sweet? If yes, how sweet is it?).* These two functions can be measured in several ways. Detection thresholds reflect the minimum concentration at which a taste can be detected. Meanwhile, discrimination is measured by recognition thresholds that reflect the minimum concentration at which the quality of a taste can be identified. **Taste intensity** is the perceived strength of a suprathreshold concentration of a taste – how sweet something is. Meanwhile, rewarding aspects of taste can be measured using different experiments which test the pleasure obtained from taste, (often referred to as the pleasantness, palatability, or reward value of taste). Pleasure is thought to drive the motivation or inhibition of ingestion. The **reward domain** of taste and eating behaviour can further be subdivided into appetitive and consummatory components. The appetitive component, or wanting, refers to the effort one is prepared to go to in order to get the reward – searching or buying (*How much effort am I ready to put in to gain some chocolate? How much am I prepared to spend?)* The consummatory component, or liking, describes the reward obtained when the food is in the mouth, which can be measured by voicing appreciation, facial expression, and swallowing (*How much do I like this chocolate?)* Liking in itself is not enough of a motivation to consume food. Consumers must also possess sufficient drive to

acquire it, and this drive comes from the desire to consume a specific food item (246). A further component of taste is referred to as the **physiological domain** (247) which covers what happens in the body after the food is consumed, including salivation or insulin response following ingestion.

The **consummatory** and **appetitive** responses (**liking** and **wanting**, respectively) of the taste reward domain are believed to change after RYGB surgery. Using visual analogue scales (VAS), RYGB patients considered pictures of high-calorie food as being less appealing and thought that sweet and fatty foods such as ice cream were a good deal less palatable (223). The responses of LGB participants did not reflect this. To assess the appetitive reward value of food through behavioural experiments, the progressive ratio task test can be used. In this experiment, subjects must work progressively harder to earn a food reward. It was found that post-RYGB study participants were much less motivated to earn rewards than participants who had received no surgical interventions, who were still willing to work harder for sweet rewards (248). RYGB patients experience unpleasant physiological responses to high sugar and high-fat foods. They may experience a reaction known as dumping which can produce nausea, abdominal cramps, hot flushes and postprandial hypoglycaemia. This may lead to a form of learned behaviour that manifests itself as an aversion to refined carbohydrates, fats and sugars, which are known to be factors that cause dumping (249). It has been hypothesised that this may be one reason for the clinically observed changes in taste preference, driving RYGB patients away from sugary foods, although dumping symptoms do not usually occur long term in RYGB.

1.2. Summary of introduction and relevance to thesis

Obesity and T2DM are conditions increasing in international prevalence. Pharmacotherapy for obesity is limited and medication for T2DM can lead to further weight gain. Meanwhile, losing weight through lifestyle changes has been shown to resolve the metabolic effects of obesity. Recent evidence shows that metabolic benefits following diet-related weight loss are similar to those seen in patients who had lost the same amount of weight after RYGB surgery (103). Moreover, diet and weight loss can induce remission in diabetes, improving the quality of life for patients who have lost a significant amount of weight (6, 115). However, weight loss is difficult to maintain through lifestyle choices alone, and it takes longer to achieve the same significant weight loss compared to RYGB. Clinical data suggest that weight loss is usually associated with hunger when calories are restricted, producing compensatory mechanisms that lead to weight regain in 80-90% of individuals (119, 250). In a modern lifestyle, the abundance of highly palatable food influences eating patterns and makes the restriction of calories an unachievable goal for many people. Losing weight through dieting and maintaining that loss is therefore challenging without associated alterations in eating behaviour and reward eating. The reduction of appetite and changes in preferences observed after RYGB on the other hand may explain its efficacy for long-term weight loss and the resolution of metabolic effects caused by obesity.

Long-term studies show that bariatric surgery – particularly RYGB – is more effective than medical therapy for controlling T2DM (175). RYGB leads to the remission of T2DM, and the elevation of gut hormones after surgery is a key factor in this process. Changes in post-surgical gut hormone levels, particularly the increased secretion of appetite suppression hormones such as GLP1, OXM, and PYY (GOP), have been suggested as a potential mechanism by which improved insulin secretion and rapid resolution of diabetes can be achieved in the early post-surgical period for people living with T2DM after RYGB (251). The mechanisms underpinning

weight loss after RYGB include behavioural and changes in brain reward responses to food, as well as changes in food preference, all of which can facilitate alterations in eating habits and a move towards healthier options (252). However, the RYGB procedure has limitations and is not universally suitable or without risk. It is not a feasible proposition to operate on everyone living with obesity or T2DM due to the finite nature of healthcare resources. Not all people who may be eligible for bariatric surgery have access to relevant facilities, especially as obesity is more prevalent in socio-economically disadvantaged areas and most bariatric surgery (outside the **UK**) takes place in the private medical sectors of developed countries. Finding safe and effective alternatives to RYGB for sustained weight loss is therefore crucial. Moreover, understanding the different underlying mechanisms that account for the success of RYGB, may translate into more affordable and accessible non-surgical interventions for both obesity and T2DM. Assessing the change in eating behaviour and taste preferences seen after RYGB and comparing them to other interventions will aid the development of better strategies to improve dietary advice offered to patients with obesity and develop new treatment targets.

1.2.1. Overall aims of this thesis

- To investigate the acute and chronic effects of the Roux-en-Y gastric bypass (RYGB) on eating behaviour, **reward drive to eat** and psychological status of people living with obesity and T2DM
- To investigate the impact of VLCD in comparison to RYGB, on eating behaviour, reward drive to eat and psychological status of people living with obesity and T2DM
- To investigate the effects of a chronic combined subcutaneous infusion of GLP-1, OXM and PYY (GOP) to match the level we see after RYGB on food intake, eating behaviour and taste preferences in people with obesity and type 2 diabetes.

1.2.2. Hypotheses

1. Roux-en Y Gastric Bypass has a favourable effect on eating behaviour, the reward drive to eat and food intake in both the short and long term.
2. Very Low-calorie Diet has a different, and less favourable effect on eating behaviour and the reward drive to eat compared with RYGB
3. The reproduction of postprandial elevation in gut hormones (GLP-1, OXM and PYY) may help recreate the favourable changes in eating behaviour and taste preferences seen after RYGB.

1.2.3. Chapters summaries

Chapter 1 Looks at the basis for this study, noting the increased global prevalence of obesity and T2DM. The chapter offers comparisons between various treatment approaches and points out that RYGB surgery is the most effective long-term treatment for obesity. It also discusses some of the underlying mechanisms for the success of RYGB and looks at the essential changes that follow RYGB that need to be understood and may need to be targeted to develop affordable, more accessible, and non-surgical long-term treatment for both obesity and type 2 diabetes.

Chapter 2 describes the methodology for three different study designs depending on cohort size which examine long- and short-term behavioural changes following gastric bypass surgery (RYGB), very-low-calorie diet (VLCD) and the infusion of triple anorexigenic gut hormones or a 0.9% saline placebo in people living with obesity and T2DM. More details about each study group and the result are shown in the following chapters (chapter 3, RYGB group; Chapter 4, VLCD group; Chapters 5 and 6, the infusion group).

Chapter 3 looks at RYGB patients in a longitudinal prospective study and investigates changes in eating behaviour, reward drive to eat, psychological status, health-related quality of life and food intake at baseline, three months and one-year after surgery. The results of this chapter will be used as a reference against which to compare subsequent chapters that use different interventions.

Chapter 4 investigates the impact of VLCDs, comprising a complete meal replacement diet, on eating behaviour, the reward drives to eat, psychological status, health-related quality of life and food intake in comparison to the RYGB group from Chapter 3. This VLCD study was designed as a prospective interventional study in which participants were asked to follow a diet of 800 kcal/day for one-month. Assessments were performed pre-VLCD and reviewed on the last day of the VLCD and at two-month after the diet ended.

Chapter 5 forms part 1 of the gut hormone infusion study, in which the impact of chronic subcutaneous infusions of three anorexigenic gut hormones GLP-1, OXM, PYY (referred to as GOP) was studied in terms of eating behaviour, the reward drive to eat, psychological status, health-related quality of life and food intake in comparison to the RYGB group from Chapter 3. The process followed a prospective single-blind observational study, and assessments were performed at baseline level, then reviewed on the last day of the one-month infusion and two-month post-infusion.

Chapter 6 forms part 2 of the gut hormone infusion study and examines GOP as a possible mediator of change in taste functions. The study aims to investigate changes in taste perception following one-month of GOP or the placebo. The results were compared with the postoperative literature in which alterations in taste preferences following bypass surgery were observed.

2. CHAPTER TWO:

MATERIALS AND METHODS

The studies included in this thesis form part of a longitudinal prospective study referred to as the Roux-en-Y Gastric Bypass (RYGB) study (NHS HRA REC reference number13/LO/1510; ClinicalTrials.gov NCT01945840) that investigated the effects of three weight management interventions; a surgery (RYGB), a diet (VLCD), and a triple subcutaneous gut hormones infusion of GLP-1, OXM and PYY (the 'GOP infusion') on people living with obesity and T2DM or impaired glucose regulation in four parts. **Part 1** studied the participants before and after RYGB surgery at intervals over a 10-year to understand changes in outcome that occur after surgery, and these participants formed a reference group. This part of the larger study is included in this thesis for the measured factors for up to one-year and the study is still ongoing. **Part 2** of the study was a preliminary Dose-Finding study for participants with obesity that was designed to define dosing strategies for a combination of anorexigenic gut hormones (GOP) that were aimed at mimicking postprandial RYGB levels. Part 2 of the RYGB study is not included in this thesis. **Part 3** compared the effects of VLCD and GOP over a month, using comprehensive profiling parameters. This part of the RYGB study is included in this thesis for the measured factors. **Part 4** makes up the final part of the RYGB study and was designed to assess the effect of individual peptide infusion and the combined infusion of two peptides on glycaemia and energy intake relative to the combined GOP infusion. This part of the study is not included in this thesis. The focus will be on the parts that were included in the current thesis only (part 1&3) and for more details about the RYGB study see Tan et al. (2017) and Behary et al. (2019) (1, 197). All participants provided written informed consent and were advised of their option to withdraw from the study at any point without providing a reason. Ethical approval was obtained from the West London Research Ethics Committee, and the study was conducted according to the principles of the Declaration of Helsinki.

2.1. Recruitment of trial participants

All study participants met the NICE criteria for bariatric surgery and fell into three groups according to the intervention they had received: RYGB, VLCD or GOP/placebo (infusion groups). Eligible participants for the VLCD and the infusion groups were recruited through advertisements on the Imperial NHS Trust research website and in the *Metro* and *Evening Standard* newspapers as well as via posters, GP practices and diabetes clinics. This added a potential source of selection bias because it is likely that participants who chose RYGB surgery varied from those who chose to follow VLCD or to have the infusion preoperatively, possibly affecting their post-operative outcomes. However, the groups and participants were similar in many ways, including pre-and post-operative demographics, obesity-related co-morbidities, and having no history of eating disorders assessed by the Sick, Control, One stone, Fat, Food (SCOFF) questionnaire and the Dutch Eating Behaviour Questionnaire (DEB-Q). To accurately compare the other groups with the surgical group, strict eligibility criteria were applied in the same way to all the study groups. The recruitment process was completed by the study team that contained medical doctors, a nurse, a psychiatrist, and a dietitian. I was the main dietitian in the team, and I ran all the dietary sessions and follow-up visits with the participants in all study groups. Every team member was trained to follow the same protocol and was able to run the study, recruit and be part of the screening.

2.1.1. Inclusion and exclusion criteria

- ***Inclusion criteria***

- Male or Female
- Aged 18 to 70
- BMI of $\geq 30 kg/m^2$
- Eligible for bariatric surgery under NHS criteria (106)

- Diagnosed with impaired glucose regulation or T2DM, according to WHO 2011 criteria. These criteria are as follows: Diabetes: Fasting Plasma Glucose (FPG) ≥126 mg/dL (7.0 mmol/L) or oral glucose tolerance test (OGTT) 2-hour Plasma Glucose (PG) ≥200 mg/dL (11.1 mmol/L). Impaired fasting glucose (IFG): FPG 110 mg/dL to 125mg/dL (6.1 to 6.9mmol/L) and OGTT 2-hour PG < 140mg/dL (< 7.8mmol/L).
- Diabetes should be stable and controlled through diet or one oral hypoglycaemic agent, with HbA1c <9.0% (<75 mmol/mol)

- ***Exclusion criteria***

To achieve relative comparability between subjects, the following criteria of exclusion were used:

- Pregnant or breastfeeding during the study and thus considered ineligible to undergo bariatric surgery or receive a hormonal infusion
- Smokers, due to risk-factor management for surgery and because smoking is known to suppress appetite and decrease taste perception
- Those without access at home to a telephone or other factors likely to interfere with the ability to participate reliably in the study
- Medical, psychological, or other conditions, or the use of medications, including over-the-counter products, which would either interfere with the study or potentially cause harm to the participant
- A history of eating disorders or restrained eating habits was screened for by the SCOFF (253) and the Dutch Eating Behaviour Questionnaire (DEBQ) (69, 70) and confirmed by psychiatric assessment.

All study activities were conducted at the NIHR/Wellcome Trust Clinical Research Unit Facility at Hammersmith Hospital.

2.2. Outcome measures

The primary outcome measures were changes in

- Eating behaviour
- Reward drive to eat
- Psychological outcomes
- Energy Intake
- Taste (GOP only)

following the different interventions, RYGB, VLCD, and infusion (GOP or saline).

2.3. Study protocol

Study visits were conducted at the Clinical Research Facility (CRF). Participants were asked to fast for at least 10 hours and to abstain from alcohol for 24 hours prior to each visit. At baseline, participants were asked to fill in a set of eating behaviour and psychological questionnaires and a four-day food diary, a process which was repeated at three-month and one-year intervals after surgery and one-month (28 days) and two-month after the VLCD diet or the infusion groups. The duration of the follow up varied according to the study group. For the RYGB group, long term follow-up after one-year was obtained, while the larger study is still in progress. For the VLCD and infusion groups, the intervention lasted for one-month and follow up visits were made two-month (8 weeks) after the intervention (Figure 4 on Page 85). There are two reasons for the differences in the timescale for the RYGB group and the VLCD and infusion groups. Firstly, when the study was designed, and based on the literature available at the time, RYGB weight loss after three-month matched the weight loss after one-month on a VLCD, and secondly to reduce the confounding effects of an initial liquid diet regime or the physical effects from surgery. Anthropometric measurements were taken at each visit,

including body weight, waist circumference and bioelectrical impedance analysis. Sensitivity, intensity, and the reward value of sweetness were investigated for the infusion groups at baseline and one-month after GOP or placebo infusion.

2.3.1. RYGB study

This longitudinal prospective observational study of RYGB patients formed the reference group against which the other two groups (VLCD and GOP infusion/placebo) were compared. This study was aimed at investigating the effect of surgical-induced weight loss on eating behaviour, the reward drive to eat, psychological status and health-related quality of life. The RYGB surgery was performed laparoscopically by three specific surgeons at IWC, to limit any heterogeneity in a procedure that might produce different RYGB-induced metabolic effects. RYGB participants were not asked to undertake a liver-shrinking diet (a VLCD) before surgery, an approach that is commonly used in obesity clinics for 2-6 weeks preoperatively to reduce liver fat. The reason behind not giving the pre-operation diet was to investigate the exclusive effect of surgery on metabolic parameters without the interference of pre-operative calorie restrictions. The first follow-up examination of changes in eating behaviour and dietary intake took place three months (12 weeks) postoperatively. This negated the confounding effects of the initial liquid diet regime and the physical effects of surgery. At the three-month visit, participants were asked to fill in the same set of eating behaviour and psychological questionnaires that they had filled in before the operation. They were also asked to fill in a four-day food diary. The same measures were repeated one-year (52 weeks) postoperatively. See Figure 4 on Page 85 for study visit plan.

2.3.2. VLCD study

The VLCD study was a longitudinal prospective interventional study aimed at investigating the effect of diet-induced weight loss on eating behaviour, the reward drive to eat,

psychological status and health-related quality of life. Participants were asked to follow a complete meal replacement plan, **a Very Low-Calorie Diet** (**VLCD**) of 800 kcal/day for one-month (28 days) based on the Cambridge Weight Plan consisting of soups, shakes and protein bars. The Cambridge Weight Plan (254) is one of several very-low-calorie diets currently available to induce rapid weight loss. One of the reasons for choosing the Cambridge Diet is because it was designed to preserve lean body mass by providing varying amounts of high-quality protein and carbohydrates and fulfilling all daily nutritional requirements. It has been also used in the **DiRECT** study (114, 115) – that investigated whether offering an intensive programme for weight loss and weight loss maintenance would be advantageous for people with Type 2 diabetes. Participants in the current study were instructed to only consume the Cambridge Diet products and to keep well hydrated. They were reviewed pre-diet and then on a weekly basis to review progress and address any problems arising from the diet until the diet was finished. On the last day of the VLCD (day 28), the first follow-up examination of eating behaviour and dietary intake took place. Participants were seen again for a follow-up visit two-month (8 weeks) later to assess their weight loss maintenance and the subsequent effects on their eating behaviour and dietary intake. See Figure 4 on Page 85 for study visit plan.

2.3.3. Infusion study

The GOP or 0.9% saline infusion study was designed as a randomised single-blind prospective study aiming at reproducing the postprandial levels of gut hormones ($GLP\text{-}1_{7\text{-}36}$, Oxyntomodulin and $PYY_{3\text{-}36}$, also referred to as 'GOP') seen in the systemic circulation post-RYGB. The doses of gut hormones used in this study were based on an initial Dose-Finding study (NHS HRA REC reference number 13/LO/1510; ClinicalTrials.gov NCT01945840) (197), in which a combination of GLP-1 at 4 **pmol/kg/min**, OXM at 4 pmol/ kg/min, and $PYY_{3\text{-}36}$ at 0.4 pmol/kg/min (GOP) was designed to replicate postprandial levels observed after

RYGB. The tolerability and safety of the combined subcutaneous GOP infusions were also assessed in the Dose-Finding study (this study is not included in this thesis).

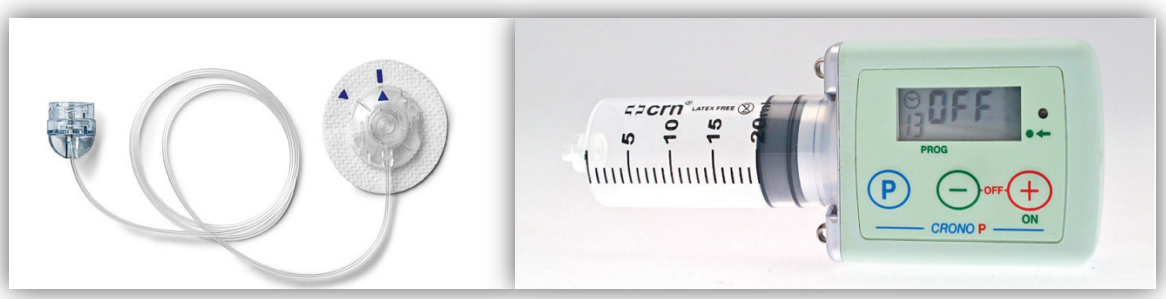
In the current study, participants for infusion were admitted by the study team to the research unit for a baseline visit and to acclimatise them to the infusion and pump for 4 days, a process that also gave them the chance to learn how to set up the pump and infusion. Participants were randomized to receive subcutaneous infusions of either a combination of three gut hormones (GOP) or 0.9% saline (the placebo). Randomisation was performed by an independent investigator using a computer table created by the Imperial College Clinical Trials Unit, based on which the infusion participants received either GOP or 0.9% saline placebo. Participants were not aware of the nature of the infusion they received and were given identical instructions on setting up the pump and the infusion by the study team. The patients were monitored for the first three days of the infusion and if any of them showed symptoms of mild nausea the infusion was stopped for at least two hours and was not restarted until the symptoms had vanished. If the nausea was moderate to severe, or if vomiting occurred, the dose was adjusted according to the participant's tolerance and increased gradually until it reached the level of the study dose. Participants were encouraged to remain hydrated during the infusion and to keep mobile within the unit, wearing the pump in their pockets or on a lanyard around the neck. Participants began the infusion an hour before breakfast and disconnected the pump half an hour after supper, giving them exposure to the infusion for approximately 12 hours each day. The pump was disconnected at night. Participants were sent home once they could prove that they could set up the infusion and the pump on their own. This was assessed by one of the team members, who asked the participants to prepare the infusion and set up the pump without any help. Participants were given cooler bags to transport the infusion and told to store the infusions in their freezers. A portable Cane Crono infusion pump (manufactured by Applied Medical Technology Ltd, Cambridge, **UK**) was used to deliver the peptides subcutaneously through an

infusion connected to a cannula that was inserted under the skin of the anterior abdominal wall using a Quickset® infusion set (made by Medtronic, Watford, **UK**) (Figure 3 on Page 64). Participants were interviewed and assessed on a weekly basis to check their welfare and to address any concerns. Infusion sites were also checked during each visit. Prior to starting the infusion, all participants had dietetic sessions at which healthy eating and lifestyle advice for weight loss was given by the same dietitian throughout the study. They were asked to follow a 600-calorie deficit diet from their total daily requirements which were calculated using the Mifflin equation. This equation has been found to provide accurate and precise REE estimates for people living with obesity (255).

Mifflin equation: *REE (kcal) = 9.99 weight (kg) + 6.25 height (cm) – 4.92 age + 166*

sex (male = 1; female = 0) – 161

Figure 3: *A Canè Crono pump and a Medtronic infusion set*



The Medtronic infusion set (left) and the pump (right) for the infusion of hormones following the body's natural rhythms.

2.4. Data collection and preparation

2.4.1. Questionnaire data

A set of questionnaires (Appendices 3-13) was completed before each intervention and were repeated three months (12 weeks) and one-year (52 weeks) after RYGB surgery and one-month (28 days) and two-month (12 weeks) after the VLCD diet or the infusion (GOP or placebo). The reasons for these differences in the measured time are outlined above, and participants were provided with an iPad onsite to complete the questionnaires. A link was emailed to the participants to complete the questionnaires at home if they were unable to complete them on-site. Scores were calculated automatically, and the data were transferred to an Excel spreadsheet for further statistical analysis.

2.4.1.1. Eating and behaviour questionnaires

2.4.1.1.1. The Dutch Eating Behaviour Questionnaire (DEBQ)

The Dutch Eating Behaviour Questionnaire (DEBQ) was developed in 1986 by Van Strien et al (70) to assess eating behaviour using a self-reporting assessment tool containing 33 questions with Likert-type scale answers ranging from 1 (never) to 5 (very often) (see Appendix 3). The questionnaire was structured to represent three subscales: Restraint (attempting to restrict food intake in order to reduce weight, including questions such as *'If you have put on weight, do you eat less than you usually do?'*); emotional motivations (emotionally-induced eating, including questions such as *'Do you have the desire to eat when you are irritated?'*) and external influences on eating behaviour (eating in response to food palatability, including questions such as *'Do you eat more than usual when you see others eating?'*). A higher score in each situation indicates a greater tendency towards the factor being measured. The three factors have been shown to influence eating behaviour (256) and affect body weight and weight-loss maintenance (72). The DEBQ shows excellent internal

consistency (Cronbach's alpha = 0.80-0.95) (71), reliability (for the total score = 0.93) construction, and validity in men and women (257). It is also suitable for use for overweight participants and those who are living with obesity (257). The three scales of the DEBQ also demonstrate excellent internal consistency (258) and reliability in bariatric surgery patients (259), although their validity is yet to be determined and should therefore be interpreted with caution (260). The DEBQ is one of the most common measures of eating behaviour and has been used in many studies of obesity and bariatric surgery (261-271).

2.4.1.1.2. Three-Factor Eating Questionnaire (TFEQ)

The Three-Factor Eating Questionnaire (**TFEQ**), which is also referred to as an Eating Inventory (EI) or the Stunkard-Messick Eating Questionnaire in some studies, is a valid and reliable psychometric tool that was developed in 1985 and contains 51 questions to measure restraint, disinhibition and hunger (272). Higher scores in each subscale indicate a greater tendency towards the measured scale. Part One of the TFEQ requires true-or-false responses to statements on **Cognitive Restraint** such as *'Life is too short to worry about dieting',* uncontrolled eating (disinhibition) such as '*Sometimes things just taste so good that I keep on eating even when I am no longer hungr*y' and eating in response to feelings of hunger such as '*Dieting is so hard from me because I just get too hungry'.* Questions in Part Two were constructed using a 5-point Likert scale ("never", "rarely"," sometimes", "often", "always") (see Appendix 4). The TFEQ was based on Herman and Mack's Restraint Theory, which suggests that restraint can lead to overeating (73, 273). The three subscales of the TFEQ have demonstrated adequate internal consistency (Cronbach's alpha of 0.87 for cognitive restraint of eating, 0.80 for disinhibition, and 0.73 for hunger) and validity across all weight groups. They are suitable to use for overweight individuals and those with obesity (71, 257). The TFEQ

is also a sensitive instrument in investigating eating behaviour. It has been validated in bariatric candidates (221) and used in several studies in the bariatric surgery population (221, 274-277).

2.4.1.1.3. Eating Disorder Examination Questionnaire (EDE-Q)

The Eating Disorder Examination Questionnaire (EDE-Q) contains 32 questions derived from the Eating Disorder Examination interview (278). The EDE-Q measures various categories of eating behaviour and eating-disorder psychopathology over a 28-day, including dietary restraint (trying to restrict food intake either successfully or unsuccessfully) and preoccupation with concerns about shape, weight and eating. Examples of dietary restraint questions are *'Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight (whether or not you have succeeded)?'*, weight concern questions such as *'Have you had a strong desire to lose weight?'*, shape concern questions such as *'Have you felt fat?'* and eating concern questions such as *'Have you had a definite fear of losing control overeating?'* (See Appendix 5). A higher score in each area indicates a greater tendency toward the measured factor. The scale has been validated in detecting eating disorders and their psychopathology in both the general population and candidates for bariatric surgery (279-281), and was found to be adequately reliable (282-284). After RYGB, patients are instructed to change some of their eating patterns, such as reducing portion sizes, increasing meal frequency, eating smaller amounts of food, and chewing their food more thoroughly before swallowing. Some patients with eating disorders before bariatric surgery may develop pathological eating behaviour such as self-induced vomiting to control weight and shape (281), while others may experience involuntary vomiting and restrain their intake for a few weeks postoperatively. The EDE-Q differentiates between involuntary behaviours and those that are associated with eating disorder psychopathology driven by excessive concerns about shape or weight. The EDE-Q was found to yield acceptable internal consistency for the global and subscale scores (Cronbach $\alpha = 0.71$-

0.91) (285). It was also found to have good reliability and convergent validity in bariatric populations (286).

2.4.1.2. Food reward questionnaire

*2.4.1.2.1. Power of Food Scale (**PFS**)*

The Power of Food Scale (PFS) is a 15-item questionnaire developed to measure the psychological effects on food consumption of living in a food-rich environment (287). The questionnaire measures the reward drive to eat palatable food, rather than the actual consumption of palatable foods, based on three suggestions of food proximity: questions on food available in the general environment such as *'I find myself thinking about food even when I am not physically hungry'*; questions on food available but also physically present but not yet tasted Including '*When I know a delicious food is available, I can't help myself from thinking about having some'*, and food anticipated but not ingested such as *'Before I eat a favourite food my mouth tends to flood with saliva'* (288). Participants are asked to respond to items on a five-point Likert scale, ranging from 1 (I don't agree at all) to 5 (I strongly agree) (see Appendix 6). The total score for the PFS is calculated from the mean of all items. The aggregated score of the three domains was found to reflect high internal consistency ($\alpha = 0.91$) and good test-retest reliability ($r = 0.77$), and was also found to be better than the one domain model (288) in restricting respondents' attention to a single PFS score. A higher score reflects a higher control or power of that food over an individual. A score of between 3.7 and 5.0 indicates that the individual is frequently preoccupied with food and at risk of losing control through overeating, while a score of between 2.4 and 3.6 indicates that the individual is somewhat preoccupied with food and is likely to have a problem with obesity. A score of less than 2.3 indicates that the individual is unlikely to be preoccupied with food. The PFS has been validated using cross-sectional designs and has been linked to overeating and obesity (287,

289-291). The scale can be used to study eating behaviour after bariatric surgery, and differences between homeostatic and reward drive to eat (292-294).

2.4.1.3. Psychological status questionnaires

2.4.1.3.1. The Beck Depression Inventory (BDI-II)

The BDI-II is a sensitive psychometric test that is widely used to measure the presence and severity of depression and anxiety over a two-week (295). It consists of 21 questions with a maximum rating of 63 points and is made up of items relating to the physical symptoms of depression, including fatigue, cognition (such as feelings of being punished) and hopelessness. Examples of items in BDI-II include *'I am dissatisfied or bored with everything'* (see Appendix 7). Cut-off scores used are: 0-13, indicating minimal depression, 14-19 (mild depression), 20-28 (moderate depression), and 29-63 (severe depression). The BDI-II has been used extensively in the context of obesity (295-297) and has demonstrated good internal consistency, test-retest reliability and construct validity with clinicians' ratings of depression (280). It has been found to be a good way of screening for clinical depression in the bariatric surgery population (298, 299) and to demonstrate excellent internal consistency (Cronbach's alpha of 0.90), convergent and criterion-related validity in the same population (300). The BDI-II will be used in this study to measure the levels of depression and anxiety before and after different obesity interventions.

2.4.1.3.2. Behavioural Inhibition and Activation System (BIS/BAS) scales

The Behavioural Inhibition and Activation System (BIS/BAS) scale is a 24-item tool used to measure sensitivity to punishment and reward (301) (see Appendix 8). The scales were based on the Reinforcement Sensitivity Theory (Gray's Theory), which hypothesized that behaviour is mediated by two independent neurobiological systems working in an inverse relationship to

guide human emotion, behaviour, and motivation. These are the behavioural inhibition system (BIS) and the behavioural activation system (BAS) (302). The BIS is thought to be related to inhibition behaviour or the inhibition of responses to avoid negative or painful outcomes (avoidance motivation). An example of a BIS question is *'I worry about making mistakes.'* The BAS, on the other hand, is based on sensitivity to the anticipation of pleasure, approach motivation and reward or non-punishment behaviour. An example of a BAS question is *'When I'm doing well at something, I love to keep at it'*. The BIS/BAS scale measures individual reward sensitivity in this study. The questionnaire consists of one BIS scale and three BAS subscales, namely Drive, Reward Responsiveness and Fun Seeking. All the subscales of the questionnaire are found to have good internal consistency reliabilities (0.66-0.76) (301). The questionnaire does not ask how often the respondent experiences anxiety; instead, it asks whether they are likely to experience anxiety in specific circumstances. The BIS/BAS scale seemed a good choice in a study aimed at identifying sensitivity to punishment and reward because the scales could be used to assess experimental situations in which punishment, or a reward were anticipated. Individuals high in BIS sensitivity reacted with greater levels of nervousness when punishment was expected, while those high in BAS sensitivity reacted with greater happiness when a reward was anticipated. The scale has been psychometrically validated to produce consistent and reliable results (301) across different cultures (303), although it becomes less responsive with age (304). It has been used in several obesity and bariatric surgery studies (305-308), but it has not been validated in these populations yet, so results should be interpreted with caution.

2.4.1.3.3. Hospital Anxiety and Depression Scale (HADS)

The **HADS** is a 14-item clinical tool used to assess symptoms of depression and anxiety levels in hospital patients by removing the physical symptoms and focusing on psychological signs

and symptoms. It is therefore considered to be un-confounded by medical conditions (309) (see Appendix 10). Items are scored according to cut-off parameters: 0-7 is normal; 8-10 is borderline abnormal, and 11-21 is abnormal (310), and the cut-off score for each subscale is ≥ 8. The tool is considered acceptable and reliable for use in psychiatric, non-psychiatric and general populations (311), has been used in many bariatric surgery studies (312-314) and has been produced in several languages (315-317) to identify and quantify depression and anxiety (318, 319). The HADS is considered well suited for detecting mood disorders among individuals with obesity and has shown a good rate of responsiveness to change in patients operated on for morbid obesity (320). Its validity and reliability have been widely accepted for in- and outpatients in a variety of countries and medical settings (321). There was a high degree of consensus between individual scores on the HADS and formal psychiatric interviews, indicating that the screening ability was robust (322), and strong psychometric properties have been demonstrated (318).

2.4.1.3.4. Barratt Impulsivity Scale (BIS)

The Barratt Impulsivity Scale (BIS) (323) is a tool containing 30 statements that are widely used to measure impulsiveness, such as *'I act on impulse'* (see Appendix 9). A higher score represents a higher impulsivity rate, and impulsivity represents a tendency towards unplanned actions – whether the stimuli is external or internal – without caring about any possible negative consequences (324). The BIS includes three subscales that are used to assess impulsivity: these represent attentional impulsivity (inability to focus attention or concentrate), motor impulsivity (acting without thinking) and unplanned impulsivity (lack of future orientation or forethought) (325, 326). An association has been found between impulsivity and obesity which has been linked to overeating (327), with attentional impulsivity being most consistently related to activities that are associated with overeating (328). Participants living with obesity

or who are overweight are more impulsive in their approach to behavioural tasks (329, 330) and measure higher on the questionnaire (329, 331) than normal-weight participants. In another study with a larger sample size and a wide range of BMI measurements, it was found that attentional and motor impulsivity were indicative of a higher BMI. Using the Barratt scale in the current study helps when it comes to investigating impulsivity levels in people with obesity following different obesity interventions. The scale was been developed based on psychopathology with a Cronbach's alpha internal consistency of 0.83 for the total score and test-retest reliability at one-month of .83 (Spearman's Rho) (325). Several bariatric studies used the BIS scale to assess the post-operative group and found that it has good internal consistency and a potential clinical utility for measuring impulsiveness among selected patients (308, 332-334).

2.4.1.4. Health-related quality of life (HR-QoL) Questionnaires

In the general population and treatment-seeking participants – especially among those seeking bariatric surgery – increased BMI is associated with impairment in HR-QoL in both the obesity-specific Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-Lite) and generic (SF-36) instruments (335-345). The current study, therefore, uses the IWQOL-Lite alongside the SF-36 questionnaire to evaluate the relevant improvements from pre- to post-intervention in each case.

2.4.1.4.1. Short-Form 36 Health Survey Questionnaire (SF36)

The SF-36™ Health Survey (346) is an internationally validated measurement that scores the generic health-related quality of life across 8 dimensions of functionality: physical functioning, role limitations due to physical problems, bodily pain, vitality, general health, social functioning, role limitations due to emotional problems and perceptions of mental health (347,

348) (see Appendix 12). The first four dimensions can be broken down further into physical components, while the last four can be grouped to provide a mental component score (349). Scores range from 0-100, with higher scores indicating better health status. The SF-36 was designed for use in clinical practice and research, health policy evaluations and general population surveys, is applicable and valid across all age groups (350, 351) and has been shown to have good constructional validity, high internal consistency and high test-retest reliability (352, 353). It also has a satisfactory validity rating in a wide range of medical conditions, including severe obesity (335, 354-359). Bariatric surgery causes a substantial weight loss, leading to changes in HR-QoL and SF-36 surveys (360). The survey was listed as one of the instruments used in evaluating HR-QoL in bariatric patients in a systematic review. It is now administered by the International Bariatric Surgery Registry (354, 356, 359, 361-363). According to experts, the SF-36 questionnaire is a very useful tool for evaluating clinically relevant improvements from pre- to post-interventions (351), but a number of studies have found that the mental domain of the SF-36 is relatively insensitive to changes in body weight over time (360, 364-367). This is true for population samples (339), treatment-seeking patients with obesity (368), and patients with morbid obesity pre-surgery (368).

2.4.1.4.2. Impact of Weight on Quality of Life-Lite (IWQOL-Lite)

The IWQOL-Lite is a validated and reliable measure that specifically gauges the impact of obesity on weight-related quality of life in normal-weight and overweight populations, including patients presenting for bariatric surgery (369, 370). Several studies used the IWQOL-Lite to assess bariatric surgery patients (354, 361, 362). The questionnaire contains 31 questions categorised under five domains: Physical Function, Self-esteem, Sexual life, Public Distress and Work. Each domain has a score, and scores are added to provide a total. Scores range from 0-155, and higher scores indicate poorer HR-QoL (see Appendix 11). All five

domains have been found to be significantly correlated with changes in weight (371). The IWQOL-Lite questionnaire is considered preferable to a generic instrument as it provides a measurement that displays greater content validity and a better attribution factor (health as a direct reference to obesity). The IWQOL-Lite was found to yield an acceptable internal level of consistency for overall total and subscale scores (Cronbach $\alpha = 0.63\text{-}0.87$) (285).

2.4.1.5. Behavioural change questionnaires

2.4.1.5.1. Alcohol Use Disorders Identification Test (AUDIT)

The Alcohol Use Disorders Identification Test (AUDIT) (372) was developed by the World Health Organisation (WHO) and shows well-demonstrated reliability and validity in assessing alcohol use and its consequences within the past 12 months (373, 374) (see Appendix 13). Regular alcohol consumption is characterised as consuming alcohol at least twice a week. AUDIT is a questionnaire that includes 10 items and represents the gold standard assessment tool for identifying early signs of harmful drinking (373, 375). Each question has four response choices, which are totalled to obtain an overall score. A score of 8 or over is associated with harmful or hazardous drinking, and a score of 13 or more for women and 15 or more for men indicates alcohol dependence. The measures demonstrate good levels of reliability and convergent validity coefficients for assessment of alcohol use in bariatric surgery populations (286, 299, 376, 377). The scale was found to have an excellent internal consistency ($\alpha = 0.82$) (378). According to national guidelines (379), active alcohol misuse is a contraindication for bariatric surgery, and alcohol should be used with severe caution, if at all, after surgery due to pharma-kinetic changes that render it more intoxicating and can contribute to the onset of alcohol-related problems (376). Most alcohol use disorders (**AUD**) were displayed by patients following their second postoperative year. Understanding the onset and prevalence of AUD in

bariatric surgical patients is critical to providing appropriate counselling and treatment (380, 381).

2.4.2. Dietary food record

Food diaries provide validated dietary records that may be useful in epidemiological or clinical research that provides important information about the quantity and composition of food consumed, and the regularity and frequency of eating. They are often used to estimate an individual's or a population group's current diet, as well as to identify groups that are at risk from malnutrition. This method is less reliant on participants' memory than other retrospective measures such as 24-hour food intake recall and allows a comprehensive investigation of diet factors that impact health outcomes. In this study, participants were given food diaries with detailed written instructions to record all food and drink consumed over four days, preferably two weekdays and two weekend days. Eating categories were defined as follows: early morning, breakfast, during the morning, midday, during the afternoon, evening meal, during the evening and bedtime snacks. Participants were asked to provide details of cooking methods, brand names and portion sizes. To help participants estimate portion size, some guidelines for describing food and drink were given, along with an example of a full day's dietary record. Participants were also asked to complete a selection of questions at the beginning of the food diary relating to the type of milk, bread and fats they usually consumed (see Appendix 14). The completed food diaries were returned via email, post or delivered personally to the research facility. Food diaries were collected at three time-point: at the beginning, at the end, and at the follow-up period for each intervention (see Appendix 14). The same food diary was used in the unit in a previously published study (197).

2.4.2.1. *Data preparation for food diaries*

Information taken from the food diaries was translated into estimated food and nutrient intake data, and was calculated and analysed using a Dietplan7 nutritional software programme (Forestfield Software Ltd, Horsham, **UK**) based on the Airwave Health Monitoring Study standard dietary coding protocol (382). An average intake figure (kcal/day) was calculated using the total energy intake divided by the number of days covered in the diary. The intake of macronutrients (expressed as a percentage of overall energy intake) was then calculated based on macronutrient grams, carbohydrate and fat totals, alcohol and protein recorded multiplied by the corresponding Atwater factors (kcal/g) of 4, 9, 7 and 4 for carbohydrate, fat, alcohol and protein respectively. Macronutrients were reported as percentage contributions to total daily calorific intake.

2.4.3. Taste test data

The taste test was conducted only in the infusion group (GOP or saline) before the infusion started and after one-month on the infusion (the last day of the infusion). The taste test measures sweet taste detection, taste intensity and consummatory taste reward using the methodology described by Bueter et al. (2011) (232). Tests were conducted in the morning after overnight fasting for 12 hours. The same brand of still natural mineral water was used for all test sessions.

2.4.3.1. *Taste detection sensitivity study*

Changes in taste were measured with a sweet taste detection test using the constant stimuli method of sucrose detection sensitivity (232). After fasting overnight, infusion participants were asked to evaluate seven different sucrose concentrations to determine sweet detection thresholds pre-and post-infusion. All solutions were prepared using sucrose from Sigma-Aldrich, Dorset, **UK** and Caledonian Still Natural Mineral Water bought from Sainsbury's

Supermarkets Ltd, London, **UK**.[1] The seven sucrose concentrations were prepared using seven different solutions (S) on the test day, each containing specific volumes of sucrose (S1=0.22g, S2=0.64g, S3=1.28g, S4=2.57g, S5=5.13g, S6=10.26g, S7=30.78g) dissolved in a fixed amount of still water (300 ml). These concentrations are the equivalent of 2.1, 6.25, 12.5, 25, 50, 100 and 300 mM respectively. Each concentration represented specific volumes, and 15 ml of each solution was decanted into polystyrene cups. A total of 112 cups were presented in eight blocks, with each block consisting of seven cups of water containing seven different sucrose values, offered in random order to eliminate expectation or habituation. Each concentration was represented once within each block. Participants were asked to hold the solution in the mouth for 5 seconds and swirl it around before spitting it into an empty container without swallowing. They were then asked whether the solution contained sugar or just water. Afterwards, they rinsed their mouths with mineral water (the same water that was used to prepare the solutions) for 10 seconds before moving on to the next sample. Participants' answers were recorded on a template scoresheet (Appendix 15). The test was performed before starting the infusion and after one-month (28 days) on the infusion (the last day of the infusion). Each test used different cup arrangements to minimise expectation and familiarisation.

2.4.3.1.1. Data preparation for sucrose taste detection sensitivity

The data collected during the sweet detection tests allowed us to derive a psychometric function in the form of an equation plotting the participants' performance based on the concentration of the solutions. The performance was analysed as a percentage of responses in which participants correctly detected the presence of sweetener. A 'hit' was recorded every time the participant correctly identified the presence of sweetener in the solution. A 'false alarm' (FA) was recorded

[1] pH 7.4, calcium 27mg/l, chloride 6.4mg/l, bicarbonate 103 mg/l, magnesium 6.9 mg/l, sulphate 10.6 mg/l, sodium 6.6 mg/l).

for every incorrect response. The hit rate for each sucrose concentration was adjusted to account for false alarms to produce a corrected hit rate using the following equation:

$$Corrected\ hit\ rate = \frac{P(hit)-P(FA)}{1.0-P(FA)} \quad (232)$$

Where *P (hit)* represents the proportion of solutions of a given concentration that were correctly identified, and *P (FA)* represents the proportion of solutions that were false alarms. This meant that if the uncorrected hit rate was the same as the false alarm rate, the corrected hit rate would be zero.

Concentration-response curves were produced to represent corrected hit rate values for each participant for each test (at baseline and one-month on the infusion) to provide a group of individual psychometric functions using the following equation:

$$F\ (x) = \frac{a}{1+10^{((log10(x)-C)*b)}} \quad (232)$$

Where $log^{10(x)}$ represents $\log^{10}$ concentration, *a* represents the upper asymptote of performance (the maximum is 1), *b* represents slope, and *c* represents the $\log^{10}$ concentration at 1/2a performance (EC50, which is defined as half-maximal effective concentration). The c parameter represents the threshold value as the inflexion point of the psychometric function, thereby optimally representing horizontal shifts in sensitivity. The experiment only compared the c-values of each of the participants' curves whose fit accounted for at least 85% of the variance, and these c-values were calculated using Mystat® (Systat® 12) software. The movements in *c* parameters were analysed using a mixed model analysis programme in IBM SPSS 24

2.4.3.2. *Intensity of sweet taste study*

The intensity of sweetness was tested using the methodology described by Bueter (2011) (232). Participants were asked to rate the intensity of sweetness before starting the infusion and on

the last day of the infusion (after one-month). Sucrose solutions were used to test the concentration of sucrose that is "just about right" using the "sip and spit" technique. In this technique, five ascending sucrose concentrations (S1=0g, S2=5.13g, S3=10.26g, S4=20.62g, S5=41.25g, each made up with 300 ml of mineral water) were decanted into 15 cups (15 ml in each) and tested in three blocks. Each block contained five cups of varying strengths, and each test was followed by a 15ml cup of water to cleanse the palate for the next stimulus. Participants were asked to take a sip from the cup containing the solution, swirl it around their mouths, and rate its intensity using the intensity Generalised Labelled Magnitude Scale (**gLMS**) while holding the solution in their mouths. All solutions were stored at 4°C and presented cold for testing. Solutions were prepared using the same Caledonian Still Natural Mineral Water, and each test had a different random arrangement of cups to minimise expectation and familiarisation.

2.4.3.2.1. The intensity generalised labelled magnitude scale (gLMS)

Participants were asked to rate the intensity of solutions compared to the most intense taste they had ever experienced (232). The results were plotted on a vertical analogue scale ranging from zero at the lower end rating ("barely detectable") to a maximum of 200 ("strongest taste of any kind") at the higher end. The scale was subdivided into four categories of intensity, ranging from "weak" to "very strong" (see Appendix 16).

2.4.3.2.2. Consummatory reward value of sweet taste

Consummatory taste measures intensity ratings and hedonic reward. Participants completed this test on the day the infusion started and the day it ended. Sucrose solutions were used to test the concentration of sucrose that was "just about right" using the "sip and spit" technique used in the intensity of sweetness test. Five ascending sucrose concentrations (S1=0g, S2=5.13g, S3=10.26g, S4=20.62g, S5=41.25g; each made up with 300 ml mineral water) were

decanted into 15 cups (15 ml in each) and tested in three blocks. These concentrations were the equivalent of 0, 50, 100, 200, 400 mM respectively. Each block contained five cups of different intensities, separated by cups of water (15 ml) to cleanse the participants' palates for the next sample. Subjects were asked to take a sip from the cup holding the solution, swirl it around the mouth, and while holding the solution in the mouth, rate its pleasantness using a Just about right scale (**JAR**), and the Reward gLMS scale (see Appendix 16.17).

2.4.3.2.3. The 'Just About Right' (JAR) scale

The JAR scale was used to rate the sweetness of the solution in terms of the ideal sweetness the participant would prefer in a soft drink. This was measured on a vertical visual analogue scale with a midpoint showing the ideal rating point, representing the ideal desired sweetness of a drink. This was shown as a zero value. The upper end of the scale measured sweetness with a value of up to +100 (Far too sweet), and the lower end measured the negative rating, with values going down to -100 at the lower end of the scale (Far too sour) (see Appendix 17).

2.4.3.3. *The reward general labelled magnitude (gLMS) scale*

The gLMS scale was used to rate how much the participants enjoyed the taste of the sweet solution in relation to the best taste they have ever experienced. This was plotted on a vertical scale with the ideal rating at its midpoint representing Neutral (a zero value) and measurements of the most liked taste ('Strongest like of any kind') going up to a value of +100 at the upper end of the scale, and the most disliked taste going down to -100 ('Strongest dislike of any kind') at the lower end of the scale. The scale was further subdivided into four categories in each direction ranging from 'weak like or dislike' to 'strong like or dislike' (see Appendix 18). As the intensity test and the consummatory reward test were prepared in the same way, and to reduce effort for the participants, they were asked to rate the three scales – the gLMS, JAR, and the Reward gLMS scales – at the same time while holding the solution in the mouth.

2.4.3.3.1. Data preparation for sucrose intensity ratings and consummatory reward value of sweet taste

The scaled responses were measured using a ruler, and the mean ratings for each concentration of the solution were measured and analysed. Comparisons within groups was assessed using a paired t-test on Prism 9 software.

2.4.4. Anthropometric measurements

The following anthropometric measurements were taken and/or calculated at baseline and at all follow-up visits in the RYGB, VLCD, and infusion (GOP or placebo) groups:

- Height was measured without shoes at baseline, using a stadiometer
- Body weight was measured to the nearest 0.1kg, with participants wearing light clothing and no shoes, using a bio-electrical impedance analysis device MC-780MA (TANITA Corporation, Japan)
- Percentage of body composition fat mass, fat-free mass in kg and percentage measured using the same bio-electrical impedance analysis device
- Body mass index (BMI) was calculated using the following formula:

$$BMI = \frac{Weight\ (kg)}{Height^2\ (m^2)}$$

- Percentage of weight loss was calculated using the following formula:

$$\%WL = \frac{Weight\ Loss\ (kg)}{Starting\ Weight\ (kg)}\ X\ 100$$

- Waist, hip and neck circumferences were measured using a measuring tape prior to and after each intervention. To maintain consistency, waist circumference was taken midway between the anterior iliac crest and the costal margin; hip circumference was measured at its broadest part, and neck circumference was measured at the midpoint of the neck.

2.4.5. Glycaemic management

Blood was taken at each visit from the start to the end of the trial by the study team. Glycated haemoglobin (HbA1c) concentrations were measured at baseline and at all follow-up visits. Samples were analysed by Northwest London Pathology, London, **UK** using a Tosoh G8 HPLC assay. Time since first diabetes diagnosis was collected at the screening visit. Numbers and types of diabetes medications were recorded at baseline, and any changes or discontinuations were recorded at the follow-up visits.

2.5. Statistical analysis

Continuous data were presented as mean ± standard error of the mean (SEM), while categorical data used counts and percentages or medians [interquartile range] depending on normality distribution. The Shapiro-Wilk normality test was used to check the normality of distribution. For continuous variables, paired student t-tests (to test between 2 groups) or one-way **ANOVA** (more than two groups) tests were used to produce baseline comparisons between groups. Unpaired t-tests were used for comparisons between groups, and the Mann Whitney U-test or Friedman test were used for baseline comparisons between groups if the data were not normally distributed. To obtain categorical variable values, the Fisher exact test (two dichotomous categorical variables) or the chi-square test (more than two groups) was performed. A P-value of <0.05 was considered statistically significant. Patients who failed to complete at least one of the follow up questionnaires or food diaries were excluded from the analysis. Statistical analyses were performed, and figures were generated using GraphPad Prism Version 9 (GraphPad Software, San Diego, USA) unless stated otherwise.

2.5.1. For within-group comparisons

Comparisons of averages for each parameter (questionnaires, food intake or anthropometric data) at each time point (before, after and follow-up) and for each intervention group were made by fitting a mixed-effects model if there were no missing values or a one-way **ANOVA** model if there were missing values, correcting for multiple comparisons using Bonferroni's post hoc test (overall and adjusted P-value respectively).

2.5.2. For between-group comparisons

Comparisons of mean change in scores from baseline values were calculated using before intervention scores minus follow-up intervention scores for each parameter and each subject in

each group intervention. These were then analysed using an unpaired t-test (RYGB vs VLCD, RYGB vs GOP, GOP vs Saline).

The power calculation of my study was based on a 30 per cent reduction in food intake following GOP compared to the placebo (this was the main outcome for the main study of which my study forms a part. It suggested that using 10 participants per group would be adequate to give a power of 80%.

This section of the analysis has a few limitations that should be listed. The number of participants in the study is small, although comparable with similar studies using these questionnaires to examine the changes in eating behaviour (221, 262, 268, 270), reward drive to eat (294, 383, 384), psychological status (271), health-related quality of life (354, 359, 362), as well as change in taste post bariatric surgery (232, 243, 261, 269, 385, 386) using the same tools as my study. Therefore, my study can be used to provide a basis for planning an extension to this study using larger numbers (see Chapter 7, Section 7.4 on Page 262-264).

Of the 79 participants recruited, 21 underwent RYGB, 24 followed a VLCD, and 34 received the infusion. Figure 5 on Page 86 shows the consort diagram of participant entry into studies). Some patients were excluded based on their inability to either attend study visits or adhere to the intervention, or due to unrelated medical conditions identified during the study, or their inability to complete the questionnaires or the food diary data.

Figure 4: *Study visit plan for the group interventions*

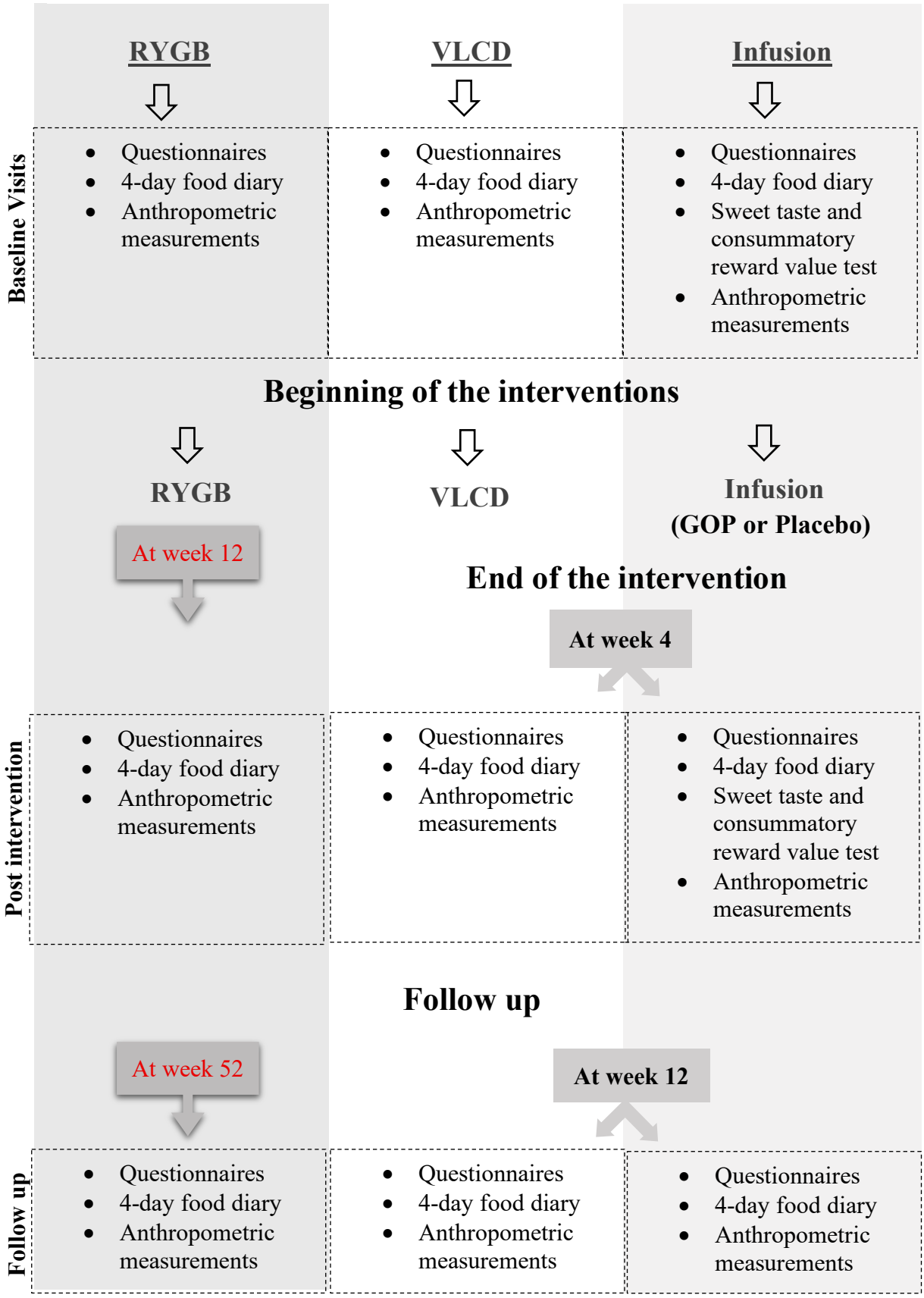
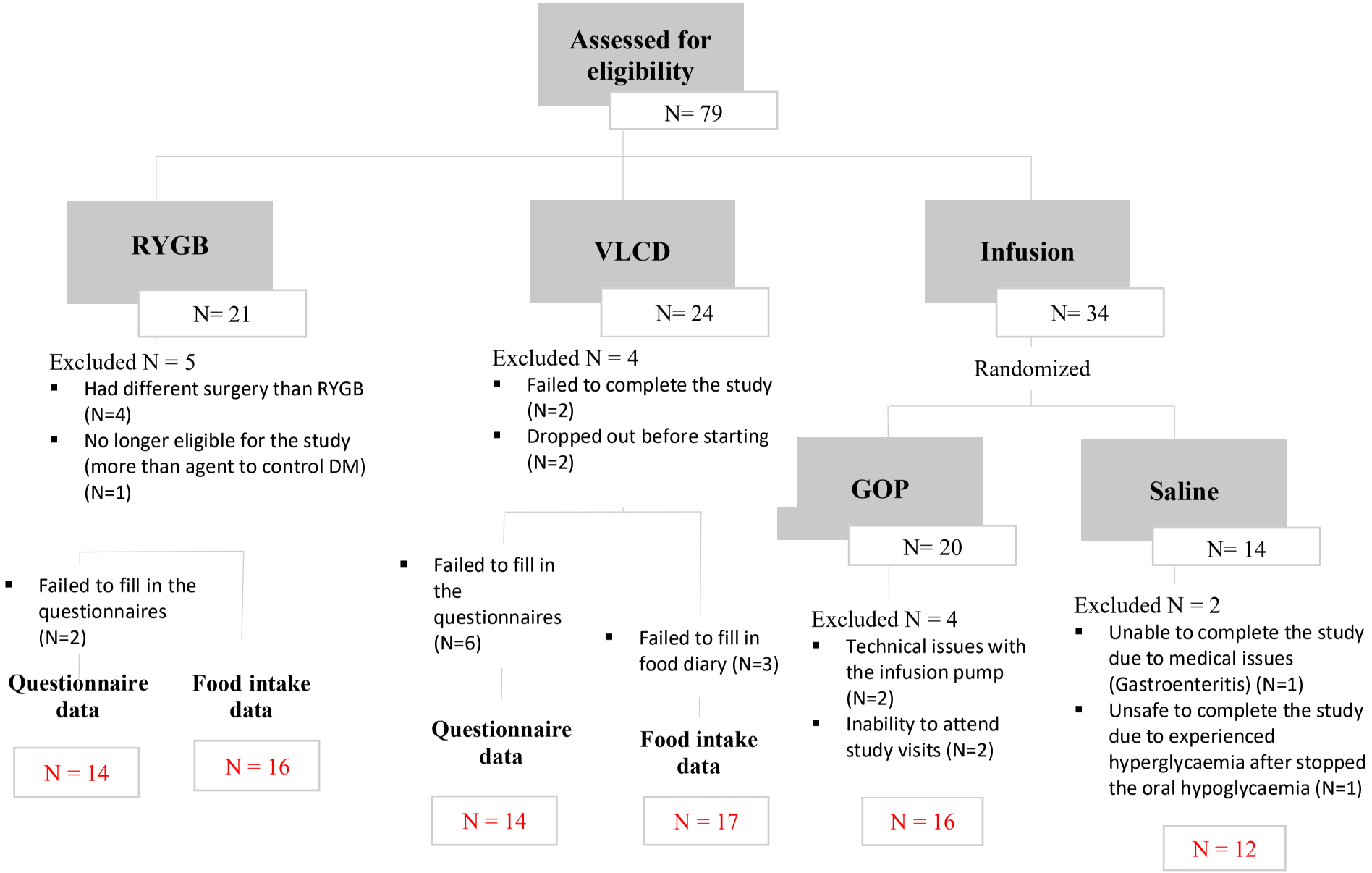


Figure 5: *Consort diagram of patient entry into studies*



Abbreviation: RYGB: Roux-en-Y Gastric Bypass; VLCD: Very Low-Calorie Diet. GOP (GLP-1,

3. CHAPTER THREE:

ROUX-EN-Y GASTRIC BYPASS

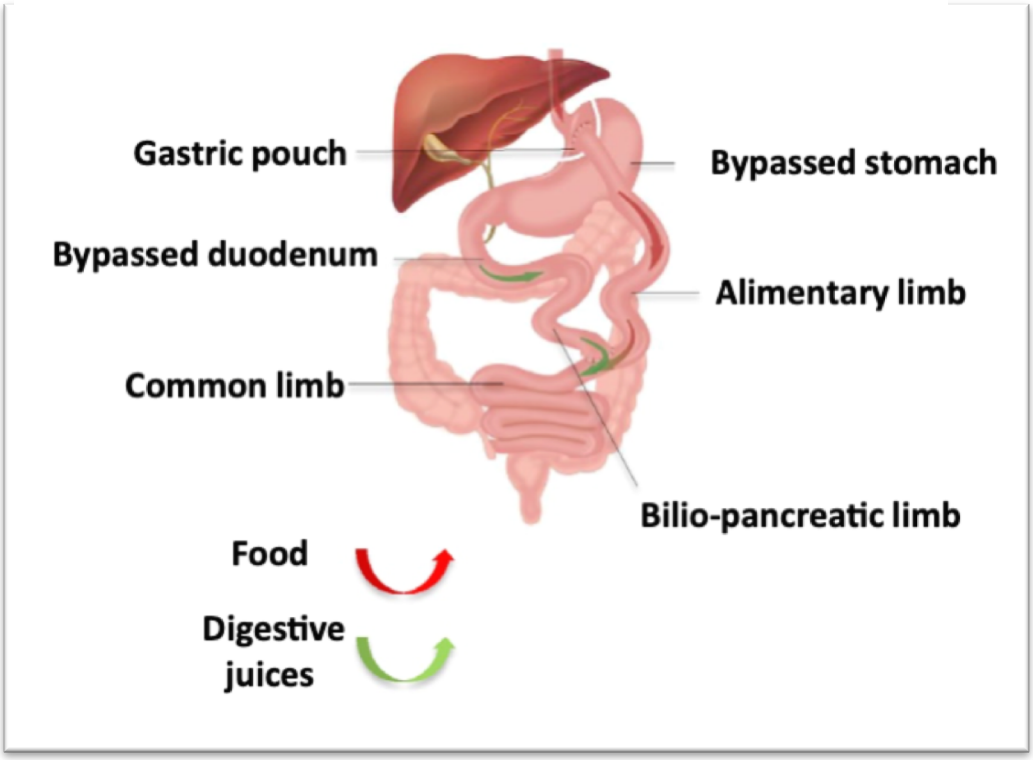
3.1. Introduction

The Roux-en-Y gastric bypass (RYGB) is currently the most effective surgical procedure for treating obesity, and results in significant and sustainable weight loss. In the early post-surgery stage the procedure results in approximately a 19% body weight loss over just three months (387) while improving remission rates in type 2 diabetes (T2DM) within a few days of surgery (388). The long-term efficacy of RYGB on weight loss and glycaemia is also accepted, with efficacy exceeding the best lifestyle or medical interventions currently available (109, 168, 170, 175). Data from the longest prospective controlled intervention trial, the SOS study, shows weight loss maintenance rates of between -32% and -27% over one-year and 15 years respectively, compared with ±3% in the control group receiving non-operational care, -13% in the banding, and -18% in the vertical banded gastroplasty groups over 15 years (109). The RYGB procedure involves partial gastrectomy and the creation of a small upper gastric pouch with an estimated size of 15-25 ml that is then linked directly to the lower part of the small intestine (the mid-jejunum) to create the Roux limb approximately 100–150 cm in length. The bypassed duodenum is attached to the distal jejunum, allowing the bile and pancreatic juices to meet the diverted food at a point lower down the gastrointestinal tract (the common channel) (170) (Figure 6 on Page 90). The newly created pouch increases the transit of food into the mid-gut, facilitating enhanced gut signalling, increased small bowel anorexigenic gut hormone concentration and neural signalling (389).

These surgically induced changes are associated with improvements in specific behavioural factors and psychological characteristics (277, 390-394), both of which are recognised as important contributors to successful postoperative outcomes (395-401). Hunger and emotional dependence eating (402) as well as eating disinhibition (defined as loss of control and consequent overeating) are found to decrease postoperatively (221, 274) in the short and long term. Improvements have also been noted in cognitive restraint eating – defined as conscious

attempts to control and monitor food intake to achieve optimal weight – after RYGB compared with preoperatively (221, 274). This appears to be a vital aspect of successful weight-loss maintenance over 2 years (270). Assessments of previous behaviour, psychological characteristics or weight-related issues are frequently conducted using self-reporting questionnaires, which may help participants manage chronic metabolic diseases such as diabetes or obesity (403). It seems unlikely that one behavioural test alone will be enough to capture the full impact of RYGB on food intake behaviour and psychological state, therefore this study used a wide range of questionnaires and evaluation procedures to gain a greater understanding of the behavioural and psychological changes underlying sustained weight loss produced by RYGB (as a gold standard treatment). This chapter investigates eating behaviour, reward drive to eat, psychosocial status, and quality of life; all of which play an influential role in long-term postoperative weight control post-RYGB.

Figure 6: *Gastric bypass surgery (RYGB)*



Source: Pucci and Batterham (2019) (404)

3.2. Research aim

To investigate the acute and chronic effects of RYGB on eating behaviour, food rewards, psychological status, health-related quality of life and food intake in people with obesity and T2DM.

3.3. Research hypotheses

1. That RYGB brings about favourable changes in eating behaviour, psychological wellbeing and food intake as observed three months after surgery
2. That RYGB decreases the reward drive to consume highly palatable food as observed three months after surgery
3. That improved eating behaviour, psychological health, and reduction in reward drive to consume highly palatable food is sustained one-year after RYGB.

3.4. Methodology

In this longitudinal prospective observational study, laparoscopic RYGB surgery was performed using standardized techniques by three specific surgeons at IWC to limit any heterogeneity in terms of RYGB-induced metabolic effects. Eligible participants were approached and recruited by the study team from the waiting list for bariatric surgery at the Imperial Weight Centre (IWC) of the Imperial College Healthcare NHS Trust. This study aims to explore the long-term (one-year) and short-term (three-month) eating behaviour, reward drive to eat and psychological changes following RYGB surgery. Participants were given time to adapt to their new dietary habits and to recover completely from surgery, so the initial follow-up examination of their changes in eating behaviour and dietary intake took place three months after surgery. See Chapter 2, Section 2.1 on Pages 57-61, for full information about recruitment, eligibility criteria, and study protocol.

3.4.1. Questionnaire data

The following questionnaires were completed before the operation and were repeated three months and one-year postoperatively (See Chapter 2, Section 2.4.1 on Pages 65-74 for more details).

3.4.1.1. Eating and behaviour questionnaires

3.4.1.1.1 *Dutch Eating Behaviour Questionnaire (DEBQ)* (70), to assess restraint, emotional, and external eating. A higher score indicates a greater tendency towards a measured response. This psychometric tool is proved to be reliable in bariatric surgery patients (259).

3.4.1.1.2 *Three-Factor Eating Questionnaire* (272) to measure cognitive restraint, disinhibition and hunger. Higher scores indicate higher levels of measured

response. The questionnaire has been found to be reliable in bariatric candidates (259).

3.4.1.1.3 *Eating Disorder Examination Questionnaire* (278) to assess the psychopathology of eating-disorder behaviour. Higher scores indicate higher levels of measured response. The questionnaire has been found to be adequately reliable and valid in bariatrics populations (279-281, 286).

3.4.1.2. Reward eating

3.4.1.1.4 *Power of Food Scale* (287) to measure the reward drive to eat more palatable food, rather than the actual consumption of palatable foods. A higher score reflects the degree of control or power food has over an individual. The scale can be used to study eating behaviour after bariatric surgery, and differences between homeostatic and reward drive to eat (292-294).

3.4.1.3. Psychological questionnaires

3.4.1.1.5 The Beck Depression Inventory (BDI-II) (295) to measure the presence and severity of depression and anxiety. Cut-off scores used were: 0–13 (minimal depression), 14–19 (mild depression), 20–28 (moderate depression) and 29–63 (severe depression). The BDI-II inventory has been found to be a good measure for screening for clinical depression, showing excellent internal consistency and validity in bariatric surgery population (298-300).

3.4.1.1.6 *Behavioural Inhibition and Activation System (BIS/BAS) scales* (301) to measure sensitivity to punishment and reward. Although the system has been used in several obesity and bariatric surgery studies (305-308), it has not been validated in these populations yet. Therefore, results should be interpreted with caution.

3.4.1.1.7 *Hospital Anxiety and Depression Scale (HADS)* (309) to measure symptoms of depression and anxiety levels in general hospital patients. Cut-off scores are: 0-7 (normal); 8-10 (borderline abnormal) and 11-21 (abnormal) (310). The HADS has shown a good level of responsiveness to change in patients operated on for morbid obesity (320).

3.4.1.1.8 *Barratt Impulsivity Scale* (323) to measure impulsiveness. A higher score represents a higher rate of impulsivity. The scale has good internal consistency. It can be used to measure impulsiveness among selected patients (308, 332-334).

3.4.1.4. Health-related quality of life

3.4.1.1.9 *The Health-related Quality of Life-Lite (*IWQOL-Lite*) Questionnaire* (369) was used to assess the impact of obesity on quality of life. Scores range from 0-155, with higher scores indicating a poorer quality of life. The IWQOL-Lite is a validated and reliable measure that gauges the impact of obesity on weight-related quality of life in both normal-weight and overweight populations of patients, including patients presenting for bariatric surgery (369, 370).

3.4.1.1.10 *Short-Form 36 Health Survey Questionnaire (SF36)* (346). The questionnaire was used to evaluate generic health-related quality of life across eight domains: physical functionality, role limitations due to physical problems, vitality, bodily pain, and social functionality, role limitations due to emotional problems, mental health and general health perceptions. Scores range from 0-100, with higher scores indicating better health status. SF-36 Survey (360) was listed as one of the instruments used in evaluating HR-QoL in bariatric patients in a systematic review, and is now used by the International Bariatric Surgery Registry (354, 356, 359, 361-363).

3.4.1.5. Substance Use

3.4.1.1.11 *The Alcohol Use Disorders Identification Test* (AUDIT) (372) was used to assess alcohol use and alcohol-related consequences. It demonstrates good reliability and convergent validity coefficients for the assessment of alcohol use in bariatric surgery populations (286, 299, 376, 377). Each question has four response choices which can be totalled to obtain an overall score. A score of 8 or over is associated with harmful or hazardous drinking, and a score of 13 or over for women and 15 or over for men points to dependence on alcohol.

3.4.2. Food intake data

Each participant was given a food diary with detailed written instructions to record all food and drink consumed over four days – preferably two weekdays and two weekend days. Participants were asked to provide details of cooking methods, brand names and portion sizes (See Chapter 2, Section 2.4.2 on Page 75, for more information about food intake data collection and preparation).

3.4.3. Statistical data analysis

A comparison of averages for each parameter at baseline, three-month and one-year intervals was made by fitting a mixed-effects model (to provide an overall P-value) and correcting for multiple comparisons using Bonferroni's *post hoc* test (to provide an adjusted P-value). Based on the results of the normality parametrical test, non-parametrical tests were performed. For the time effect of RYGB at the three time-points, a mixed-effects model was used (before, after and follow-up) using Bonferroni's correction (adjusted P-value). All statistical analyses were performed, and all figures were generated using GraphPad Prism 9 (GraphPad Software, San Diego, CA). See Chapter 2, Section 2.5 on Page 83, for more information about statistical analysis.

3.5. Results

The results of this chapter are used as a reference to compare the following chapters with different interventions.

3.5.1. Participant characteristics for the RYGB questionnaires data

A total of 21 participants were recruited for the RYGB study. Seven were excluded from the questionnaire analysis for the following reasons:

1. Three participants had their operations changed to sleeve gastrectomy, and one was given an open RYGB procedure due to technical difficulties experienced during the operation.
2. Two failed to answer the questionnaires (they were included in the food diary analysis as they provided food diaries but not in the questionnaire analysis)
3. One participant experienced a deterioration in diabetes control prior to surgery, which required the addition of multiple glucose-lowering agents for glycaemic optimisation, rendering him ineligible for the study.

See Figure 5, Chapter 2 on Page 86 for the consort diagram of patient entry into studies.

Questionnaire data were therefore available for only fourteen participants who underwent RYGB surgery. In this study, the criteria for including participants were determined by data collected from a baseline questionnaire as well as several follow-up questionnaires. If data were available from the baseline and at least one of the follow-up questionnaires, the participant was included in the final analysis. If data were available from one of the follow-up periods (three months or one-year after intervention), the participant was also included. However, participants would be excluded if there was no baseline record available, or if no data other than baseline records were available. This RYGB group was predominantly female

(85.7%), with a mean BMI of 42.4kg/m^2 and diabetes diagnosed in 79% of participants. The remaining participants were prediabetic. Two out of the fourteen were stable on long-term antidepressant treatment. The baseline characteristics are shown in Table 2 on Page 98.

Table 2: *Baseline characteristics of the RYGB participants*

RYGB	Baseline	
	"For Questionnaires data" N=14	**"For Food diaries data" N=16**
Gender (F:M)	(12:2)	(13:3)
Age (years)	46.90±3.20	48.75±3.4
Weight (kg)	116.60±6.90	115.5±6.8
BMI (kg/m2)	42.40±1.60	42.9±1.70
Waist (cm)	121.90±3.20	122.4±3.40
Hip (cm)	133.40±4.50	134±4.50
Waist: Hip Ratio	0.90±0.030	0.9±0.03
Neck (cm)	41.0±1.00	40.7±0.97
FM (%)	46.60±1.00	46.22±1.70
T2DM, n (%)	11 (79)	13 (81)
Prediabetic, n (%)	3 (21)	3 (19)
Treatment		
- **Diet only, n (%)**	5 (36)	5 (31)
- **Metformin only, n (%)**	9 (64)	11 (69)
On antidepressants treatment, n (%)	2 (14)	2 (12.5)
Systolic blood pressure (mmHg)	133.10±4.00	127.8±3.50
Diastolic blood pressure (mmHg)	74.0±4.00	72.9±2.50
Heart rate (beats per min)	76.0±2.90	77.9±3.40
HbA1c (mmol/mol)	57.50±3.80	58.13±3.70
Fructosamine (µmol/l)	252.90±10	254±8.60

Data presented as mean±SEM or median [interquartile range] for parameter do not display Gaussian distribution. A Fisher exact test was used for categorical data. Prediabetic characteristics include impaired glucose tolerance, impaired fasting glucose, or HbA1c of 6.0–6.4% (42–48 mmol/mol). Abbreviations: BMI, Body mass index; RYGB, Roux-en-Y Gastric Bypass; T2DM, Type 2 diabetes mellitus; FM, Fat mass; HbA1c, Glycated Haemoglobin

3.5.2. Eating behaviour following RYGB

Questionnaire scores showed no pathology at baseline in any of the measured variables of interest. Eating behaviour questionnaires indicated that patients from three months to one-year after RYGB had healthier eating behaviour and showed changes in eating disorder psychopathology compared with pre-surgery, with significantly higher scores for dietary restraint and lower scores for external eating and weight and shape concerns (see Table 3 on Page 101). The analysis used a mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test.

3.5.2.1. *The Dutch Eating Behaviour Questionnaire (DEBQ)*

Three months after RYGB, there was a significant overall increase in restrained eating from 2.67±0.16 to 3.48±0.26 measured on the DEBQ restraint scale (Overall, P=0.0079), and a significant reduction in external eating from 3.26±0.18 to 2.29±0.24 as measured on the DEBQ external eating scale (Overall, P=0.002). However, the reduction in emotional eating was not significant, moving from 2.5±0.27 to 2.15±0.25 on the DEBQ emotional eating scale (Overall, P=0.3). Post-hoc analysis comparing different time points showed that changes in restraint and external eating were significant at three months post-RYGB (Adjusted, P=0.007 and P=0.002 respectively) compared with pre-surgery. However, no significant difference was seen at the one-year analysis across all three subscales, although scores did not revert to the same levels as pre-surgery (Table 3 on page 101).

3.5.2.2. *Three-Factor Eating Questionnaire (TFEQ)*

There was a significant reduction in disinhibition measured by the TFEQ three months post-surgery (Overall, P=0.0009; Adjusted, P=0.013), and that reduction remained significant and was greater at one-year compared with pre-surgery (Adjusted, P=0.002). There were no significant changes in hunger and cognitive restraint subscales at any point (Table 3 on page 101).

3.5.2.3. *Eating Disorder Examination Questionnaire (EDE-Q)*

This RYGB group showed low levels of eating disorder psychopathology at baseline, measured using the EDE-Q with the highest scores out of six going to weight (3.4±0.38) and shape (3.89±0.40) concerns. Three months after RYGB, there was significantly lower weight (2.52±0.35) and shape concerns reported (Overall, P=0.02 and P=0.03 respectfully) compared with baseline figures. The reduction in weight concern remains significant for up to one-year postoperatively (Adjusted, P= 0.048). No change in any other domains (Table 3 on Page 101).

3.5.3. Reward Drive to Eat following RYGB

3.5.3.1. *Power of Food Scale (PFS)*

The PFS showed a significant reduction in reward response to food three months post-surgery (Overall, P=0.0008; Adjusted, P=0.0009). This was still present one-year after surgery (Adjusted, P=0.005) post-surgery (Table 3 on Page 101).

Table 3: *Eating behaviour and food reward questionnaires following RYGB*

Baseline N=14	**Three-month N=13**	**One-year N=11**	**Pre vs Three-month** *P*-value[a] (95% CI)	**Pre vs One-year** *P*-value[b] (95% CI)
		Eating Behaviour following RYGB		
		The Dutch Eating Behaviour Questionnaire (DEBQ)		
		Dietary Restraint (score/5)		
2.67±0.16	3.48±0.26	3.14±0.43	0.007 ** (-1.45 to -0.16)	0.20 (-1.52 to 0.59)
		Emotional eating (score/5)		
2.5±0.27	2.15±0.25	2.51±0.46	0.109 (-0.27 to 1.24)	0.56 (-1.10 to 1.14)
		External eating (score/5)		
3.26±0.18	2.29±0.24	2.41±0.34	0.002 ** (0.31 to 1.65)	0.07 (-0.14 to 1.85)
		Three-Factor Eating Questionnaire (TFEQ)		
		Cognitive Restraint (score/21)		
10.29±1.4	6.08±1.29	5.11±1.62	0.11 (-0.79 to 9.21)	0.12 (-1.23 to 11.58)
		Disinhibition (score/16)		
8.78±0.68	6.23±0.57	5.44±0.96	0.002** (0.84 to 4.27)	0.013* (0.70 to 5.98)
		Hunger (score/14)		
6.36±0.75	7.31±0.61	6.78±0.57	0.42 (-3.26 to 1.36)	0.21 (-2.77 to 1.93)
		Eating Disorder Examination Questionnaire (EDEQ)		
		Restraint (score/6)		
1.44±0.33	2.32±0.52	1.98±0.60	0.26 (-2.69 to 0.92)	0.367 (-2.32 to 1.25)
		Weight (score/6)		
3.4±0.38	2.52±0.35	1.76±0.42	0.035* (0.09 to 1.97)	0.048* (0.19 to 3.16)
		Eating (score/6)		
1.45±0.44	0.85±0.28	0.62±0.43	0.314 (-0.99 to 2.18)	0.312 (-0.87 to 2.53)
		Shape (score/6)		
3.89±0.40	3.01±0.47	2.05±0.53	0.22 (-0.37 to 2.14)	0.096 (0.06 to 1.98)

Global (score/6)				
2.5±0.37	2.18±0.33	1.59±0.40	0.290 (-0.72 to 1.40)	0.186 (-0.27 to 2.13)
Food Reward Questionnaire following RYGB				
Power of Food Scale (score/5)				
3.18±0.29	2.04±0.29	1.87±0.26	0.0009*** (0.47 to 1.81)	0.005 ** (0.31 to 2.31)

Data are displayed as mean±SEM (95% CI) for pre-RYGB, three months and one-year post-RYGB. A mixed-effects model was used to compare the averages between different time points with correction for multiple comparisons using Bonferroni's post hoc test (adjusted *P*-value) *P*-value[a] (Pre-Op vs three-month), *P*-value[b] (Pre-Op vs one-year). *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

3.5.4. Psychological and behavioural changes following RYGB

Other psychological and alcohol outcomes measured on the following scales showed no significant change in any variable measured at three-month or at one-year post-surgery:

- Impulsivity measured by *Barratt Impulsiveness Scale (Barratt)*.
- Punishment and reward sensitivity, measured by the *Behavioural Inhibition System/Behavioural Activation System (BIS/BAS) Scales*
- Anxiety and depression, measured by Hospital Anxiety and Depression Scale
- Depression symptoms over the last 2 weeks, measured by *Beck Depression Inventory (BDI-II)*
- Alcohol intake, measured by *Alcohol Use Disorders Identification (AUDIT)*

These figures were analysed using a mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test (Table 4 on Page 103).

Table 4: *Psychological and behavioural questionnaires following RYGB*

Baseline N=14	**Three-month N=13**	**One-year N=11**	**Pre vs Three-month** *P*-value[a] (95% CI)	**Pre vs One-year** *P*-value[b] (95% CI)
<u>Psychological Status following RYGB</u>				
Barratt Impulsiveness Scale (score/120)				
60.86±3.07	62.54±2.59	62.10±4.13	>0.999 (-9.43 to 6.07)	>0.999 (-10.88 to 8.39)
Behavioural Inhibition System/Behavioural Activation System (BIS/BAS) Scales				
Drive-Seeking (score/16)				
11±0.67	11.92±0.89	12.10±1.01	0.16 (-2.92 to 1.07)	0.36 (-3.68 to 1.48)
Fun-Seeking (score/16)				
11.1±0.5	12.23±0.60	11.90±0.85	0.16 (-2.47 to 0.29)	0.61 (-2.85 to 1.34)
Reward-Responsiveness (score/20)				
16.79±0.47	16.69±0.63	16.70±0.89	>0.99 (-1.29 to 1.48)	0.75 (-1.58 to 1.75)
BAS (score/28)				
20.7±0.88	21.23±0.97	20.40±1.34	0.65 (-1.92 to 0.89)	0.72 (-1.97 to 2.60)
Hospital Anxiety and Depression Scale (HADS)				
HADS-Anxiety (score/21)				
7.43±1.2	7.77±1.58	6.11±1.81	0.86 (-4.17 to 3.44)	0.14 (-1.20 to 4.52)
HADS-Depression (score/21)				
6.57±0.95	5.31±1.19	3.56±1.02	0.28 (-1.10 to 3.74)	0.08 (-1.10 to 3.74)
Beck Depression Inventory				
BDI-II (score/63)				
13±2.2	12±3	12.22±4.02	>0.99 (-10.29 to 22.95)	>0.99 (-12.32 to 13.88)
<u>Behavioural changes following RYGB</u>				
Alcohol Audit				
2.57±0.66	1.62±0.66	1.60±0.91	0.26 (-1.38 to 3.29)	0.31 (-2.16 to 4.11)

Data are displayed as mean±SEM (95% CI) for pre-RYGB, three months and one-year post-RYGB. A mixed-effects model was used to compare the averages between different time points with correction for multiple comparisons using Bonferroni's post hoc test (adjusted P-value), *P*-value[a] (Pre-Op vs three-month), *P*-value[b] (Pre-Op vs one-year). Abbreviation: RYGB: Roux-en-Y Gastric Bypass, BIS/BAS: Behavioural Inhibition System/Behavioural Activation Scales, HADS: Hospital Anxiety and Depression Scale, BDI-II: Beck Depression Inventory. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

3.5.5. Health-related quality of life following RYGB

Weight loss showed general improvements in health-related quality of life, according to the SF-36 and IWQoL scales that were used to assess this aspect. Results were analysed using a mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test (Table 5 on Page 105).

3.5.5.1. *SF-36TM health survey (SF-36)*

There were improvements in all eight areas measured using this scale, indicating improved quality of life. The general health score was significantly higher in the general health category (Overall, P=0.0451), and post hoc analysis showed a significant improvement three months post-surgery (Adjusted, P=0.02) but not at one-year (Adjusted, P=0.112). There was a significant reduction in bodily pain at three months (Overall, P=0.002; Adjusted, P=0.015) and one-year after surgery (Adjusted, P=0.001). An improvement was also observed in limitations due to physical health (Overall, P=0.004; Adjusted, P=0.007) and limitations due to emotional problems (Overall, P=0.02) (Table 5 on Page 105).

3.5.5.2. *Impact of Weight on Quality-of-Life Questionnaire (IWQoL-Lite)*

There were general improvements in the total score three months and one-year after surgery (Overall, P= 0.01; Adjusted at three-month, P=0.02; at one-year, P=0.008). The improvements in other subscales were not statistically significant in the study period (Table 5 on Page 105).

Table 5: *Quality-of-life questionnaires following RYGB*

Baseline N=14	**Three-month N=13**	**One-year N=11**	**Pre vs Three-month** *P*-value[a] (95% CI)	**Pre vs One-year** *P*-value[b] (95% CI)
		SF-36TM Health Survey (SF-36)		
		Physical Functionality (score/100)		
48.9±7.76	73.85±7.14	90.00±4.17	0.056 (-50.45 to 0.61)	0.0002 *** (-57.37 to -24.77)
		Limitations due to physical health (score/100)		
53.57±12	94.23±4.15	91.67±8.33	0.007** (-27.20 to -9.12)	0.062 (-77.78 to 1.59)
		Limitations due to emotional problems (score/100)		
61.9±10	84.62±8.10	96.30±3.70	0.055 (-49.11 to 3.69)	0.040* (-75.90 to 7.12)
		Energy/Fatigue (score/100)		
47.86±4.96	53.85±6.33	61.11±7.10	0.46 (-28.07 to 16.1)	0.144 (-34.88 to 8.37)
		Emotional wellbeing (score/100)		
70.86±5.2	64.00±7.71	78.22±7.15	0.29 (-7.67 to 21.38)	0.072 (-14.69 to -0.03)
		Social Functionality (score/100)		
62.3±7.9	69.23±7.96	90.28±4.55	0.63 (-34.72 to 20.9)	0.028* (-50.35 to -5.56)
		Pain (score/100)		
54.8±5.8	78.27±4.44	85.28±5.58	0.015* (-45.49 to -1.40)	0.001** (-48.18 to -12.74)
		General Health (score/100)		
48.39±6.34	61.25±6.01	66.25±8.00	0.02* (-27.94 to 2.23)	0.112 (-41.23 to 5.51)
		Quality-of-Life Questionnaire (IWQoL-Lite)		
		Physical Function (score/55)		
32.57±3.5	23.46±2.96	19.67±4.15	0.012* (1.87 to 16.35)	0.061 (-0.55 to 26.36)
		Sexual Life (score/20)		
23.79±2.3	21.00±2.82	16.00±3.29	0.158 (-3.67 to 9.24)	0.068 (1.24 to 14.33)
		Public Distress (score/25)		
14.57±1.5	13.00±2.14	10.00±1.95	0.417 (-1.95 to 5.09)	0.074 (-1.07 to 10.21)

		Work Problems (score/20)		
9.85±1.07	9.15±1.54	7.22±1.26	0.371 (-1.33 to 2.74)	0.078 (-0.41 to 5.68)
		IWQoL Total (score/155)		
94.57±6	77.38±10.10	61.33±9.94	0.021* (0.48 to 33.89)	0.008** (11.09 to 55.39)

Data are displayed as mean±SEM (95% CI) for pre-RYGB, three months and one-year post-RYGB. A mixed-effects model was used to compare the averages between different time points with corrections for multiple comparisons using Bonferroni's post hoc test (adjusted P-value), *P*-value[a] (Pre-Op vs three-month), *P*-value[b] (Pre-Op vs one-year). Abbreviation: SF36, SF-36 ™ Health Survey; IWQoL, Impact of Weight on Quality-of-Life Questionnaire. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

3.6. Changes in food intake based on dietary records following RYGB

Sixteen out of 21 patients were included in this food diary analysis. Five were excluded for the same reasons mentioned above for the questionnaires data (Section 3.5.1 on Page 96). Two patients failed to fill in the questionnaires data but did record their food intake and provide food diaries. They were therefore included in the food diary analysis. The baseline characteristics for dietary records data are shown in (Table 2 on Page 98) above. Changes in energy intake were investigated using a four-day food diary (Table 6 on Page 107). The total calorie intake decreased significantly (Overall and Adjusted, P<0.0001) by about 50.2% (-946kcal/day) at three months and by about 36% (-676 kcal/day) one-year post-surgery compared with the pre-operative intake levels, which were 1883±141 kcal/day. The macronutrient distributions showed no significant changes at any of the time points measured post-surgery. The largest macronutrient proportion was in carbohydrates, with around 47% at three months and 44% at one-year. There was a slight increase in protein intake at three months (+5%) and at one-year (+4%) postoperatively, compared with pre-operative levels (Overall, P=0.01; adjusted, at three-month P=0.013, at one-year P=0.26). In terms of fat, there was a non-statistically significant reduction in fat intake at three months (-6.6%) and at one-year (-4.3%) postoperatively compared with pre-operatively (Overall, P=09) (Table 6 on Page 107).

Table 6: *Changes in food, alcohol and macronutrient composition intake following RYGB*

Baseline N=14	**Three-month N=13**	**One-year N=11**	**Pre vs Three-month** *P*-value[a] (95% CI)	**Pre vs One-year** *P*-value[b] (95% CI)
		Total energy intake (Kcal/day)		
1883±141	937.0±92.79	1207±145	<0.0001 (385.0 to 1361)	0.0031 (322.7 to 1029)
		Macronutrient composition		
		Carbohydrates (% total kcal intake)		
43.85±1.57	46.8±2.7	44.40±2.55	>0.99 (-10.68 to 4.77)	>0.99 (-9.35 to 8.27)
		Protein (% total kcal intake)		
16.84±0.70	20.9±1.2	19.53±1.15	0.01* (-7.40 to -0.68)	0.26 (-6.51 to 1.15)
		Fat (% total kcal intake)		
38.9±1.70	32.3±2.5	34.58±2.49	0.1023 (-0.92 to 14.09)	0.64 (-4.24 to 12.87)
		Alcohol intake (% total kcal intake)		
0.4±0.40	0.00	0.00	>0.99 (-1.24 to 2.07)	0.47 (-2.97 to 0.79)

Data are displayed as mean±SEM (95%CI) for pre-RYGB, three-month and one-year post-RYGB. A mixed-effects model was used to compare the averages between different time points with correction for multiple comparisons using Bonferroni's post hoc test (adjusted P-value), *P*-value[a] (Pre-Op vs three-month), *P*-value[b] (Pre-Op vs one-year). *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

3.7. Anthropometric data following RYGB

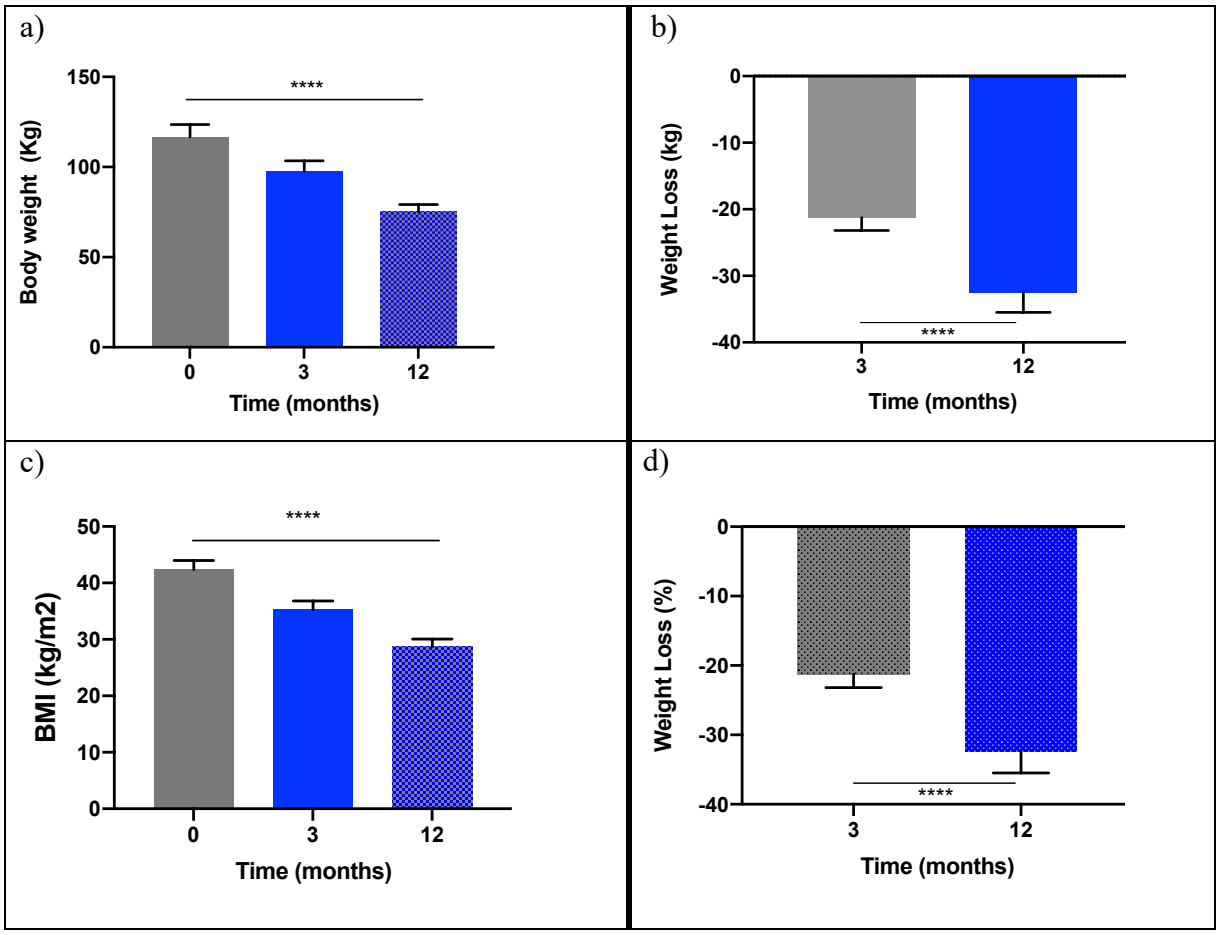
As expected, RYGB led to substantial and progressive weight loss for up to one-year after surgery (Table 7). Participants' mean body weight at baseline visit was 116.6±6.9 kg. At week 12 it was 97.55±5.9, and at week 52 it had come down to 75.09±4.1 ($p<0.0001$). A mixed-effects model was used to compare each time-point against the baseline visit. This showed a significant weight loss of -21.25±1.9kg and -32.45±3kg three months and one-year post-surgery ($P<0.0001$) or a change in body weight by -17.82±1.10%, and -29.69±1.455% respectively at these above time-points ($P<0.0001$) (Table 7; Figure 7 on page 109).

Table 7: *Changes in body weight following RYGB*

	Baseline N=14	**Three-month N=13**	**One-year N=11**	**Pre vs Three-month** *P*-value[a] (95% CI)	**Pre vs One-year** *P*-value[b] (95% CI)
Weight (kg)	116.6±6.9	97.55±5.9	75.09±4.1	<0.0001 (13.57 to 24.60)	<0.0001 (30.24 to 52.85)
BMI (kg/m^2)	42.4+1.6	32.76±2.9	28.73±1.32	<0.0001 (5.66 to 8.53)	<0.0001 (10.87 to 16.42)
	Three-month		**One-year**		
WL (kg)	-20.02±1.60		-35.28±3.03		
%WL	-17.19±0.98		-30.04±1.533		

Data are displayed as mean±SEM (95% CI) for pre-RYGB, three-month and one-year post-RYGB. A mixed-effects model was used to compare the averages between different time points with correction for multiple comparisons using Bonferroni's post-hoc test (adjusted P-value (95% CI)), *P*-value [a] (Pre-Op vs Three months); *P*-value [b] (Pre-Op vs One-year); WL (kg) and %WL were analysed with a Student Paired t-test (*P*-value[d]).

Figure 7: *Effects of RYGB on body weight and BMI throughout the study*



Data are presented as mean±SEM at three-month and one-year post-RYGB. a) A significant reduction in the absolute BW (kg) was found using a mixed-effects model with correction for multiple comparisons using Bonferroni's post-hoc test. b) Weight loss in kg using a Student Paired t-test. c) Percentage weight loss post-RYGB (%) using Student Paired t-test. d) A significant reduction in BMI (kg/m^2) using mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

3.8. Discussion

3.8.1. Summary of findings for RYGB

This longitudinal study aimed to explore the acute and chronic influence of RYGB on eating behaviour, eating reward, psychological profiles, and health-related quality of life among people living with obesity and T2DM. The study used validated and reliable sets of questionnaires. New findings were related to the reduction in the reward impact of food that was observed during the first three months post-RYGB, and which was sustained for up to one-year after surgery. There was also a long-term reduction in dietary disinhibition and weight concerns post-RYGB. There were short-term increases in dietary restraint as well as decreases in eating in response to external stimuli that remained lower than the baseline level – although not statistically significant – one-year after the operation. The results also demonstrated an overall improvement in health-related quality of life. These changes do not appear to be explained by other psychological factors such as change in depression rates or impulsivity, since the RYGB surgery showed little or no statistically significant impact in these areas. Data from the food diaries kept by the participants showed a significant long-term reduction in food intake and an acute increase in protein intake post-RYGB compared to before. No significant changes in fat, carbohydrate or alcohol intake were observed during the period of the study.

3.8.2. Reward drive to eat and food intake following RYGB

Foods that are high in fat and sugar are associated with positive effects and rewards, which are also considered to be the main challenge when treating obesity at an individual level (405). Hedonic hunger drives the appetite, promoting the enjoyment of eating as well as the anticipated pleasure that is linked to eating where there is no metabolic need. This is combined with an increased desire for food when it is either absent or considered to be prohibited (406). In such cases, people want food but do not need it. This desire is encapsulated in the form of hedonic hunger. In the current study, individuals with obesity and T2DM who had undergone

RYGB surgery showed lower levels of hedonic hunger (as measured by the PFS) at three months, which was sustained for up to one-year postoperatively compared with baseline levels. These findings suggested that the RYGB procedure reduces hedonic hunger, which might be facilitating long-term changes in eating behaviour. Evidence from behavioural studies (292, 294) as well as neuroimaging studies (223, 407-419) support this conclusion. This reduction in reward drive to eat might be mediated by various changes in the neural networks that control homeostatic and reward eating. In 2013, Ullrich et al. ran a prospective observational behavioural study that compared 44 participants pre-RYGB (mean BMI=47 kg/m2) and for 11-39 months post-RYGB (mean BMI=29 kg/m2). The study reported a reduction in post-RYGB aggregated PFS scores and favourable changes in dietary habits, as measured by a food frequency questionnaire. These changes included a reduction in the consumption of sugary snacks and beverages (292). Meanwhile, a retrospective cross-sectional study (294) compared individuals with obesity one-year post-RYGB with normal-weight individuals (pre-surgery mean BMI was 45.1, one-year= 29.5, and the normal-weight group = 22.4 kg/m2 respectively) using the same scale, and discovered that individuals exhibited a diminished drive to consume highly palatable foods (high-calorie food) post-RYGB compared to individuals with obesity who had not undergone RYGB surgery. The post-RYGB scores were comparable to groups without obesity, and the authors suggested that the operation might have the effect of normalising excessive appetites for palatable food (294). In terms of neuroimaging, several studies (420-423) showed differences in responses to pictures of palatable foods in the neural systems that regulate food intake and the reward system of individuals with obesity when compared with normal-weight individuals.

In a prospective observational study (411) that examined food reward systems using fMRI scans of 22 RYGB patients pre- and six months post-surgery, there was a reduction in BOLD response to high-calorie vs low-calorie food in the ventral tegmental area (VTA) at 6 months

in the RYGB group, but not in the VSG or the normal-weight control group. There was also a greater reduction in the desire to eat highly palatable foods following RYGB compared to before, as well as in comparison to the control group, which was mirrored in brain activity patterns (411). The increased availability of palatable food was found to be an important trigger in stimulating food cravings, disrupting appetite regulation and driving patterns of overeating in individuals living with obesity. The reduction in reward responses of hyper-palatable and hyper-caloric foods that we see after RYGB (220) may help reduce hedonic hunger (424) leading to a shift in food preferences towards a less energy-dense diet, as seen in human (425) and animal studies (426). It is interesting to note that hedonic hunger is caused by the availability of food, rather than the presence of food or its taste according to the PFS. This conclusion reflects the idea that the main impact of hedonic hunger stems from thinking about highly desirable foods rather than the compulsive eating of food that is immediately present or tasted (427).

RYGB surgery was found to be associated with a reduction in total calorie intake, changes in food preferences and fat and carbohydrate consumption as measured by 24-dietary recall methods (182). However, the literature offers a complex picture regarding the consequences of RYGB surgery on overall macronutrient intake. In the current study, there was a significant reduction in calorie intake as measured by 4-day food diary. In line with previous findings, there was a significant increase in protein intake three months postoperatively (20.9%), which remained higher than the baseline (16.8%) up to one-year after surgery (19.5%), as measured by the food diary. Increases in the percentage of calories obtained from protein three months post-surgery was in line with previous observations (274). No change in the percentage of calories obtained from carbohydrate was observed during the study period. Patients are generally advised to consume enough protein after their surgery in order to preserve muscle mass (428), improve nutrition status, increase levels of satiety and continue with their weight

loss programme (429). Meanwhile, there was a general reduction in fat intake across all the time points measured. Some studies also discovered changes in macronutrient composition and overall calorie intake post-RYGB, but although the findings varied they were not statistically significant (224, 225). Another study found the opposite, with an increase in fat intake and a decrease in protein consumption after surgery (425), while in a study by Bavaresco et al. (2010) patients reported an overall decrease in their intake of all three macronutrients (carbohydrates, fats and proteins), with no specific preference for any macronutrient after surgery (430). While there is an agreement on the reduction in food intake following RYGB, the exact impact of the surgery on the macronutrient composition of post-surgery diets remains to be determined. In the current study, it is difficult to conclude that the effect of the change in micronutrient composition in food intake – if any – is related to the variation in eating behaviour or weight loss seen in some patients after surgery. Many factors may indirectly impact the macronutrient composition of individual's preoperative and postoperative food intake, such as social and financial factors, or post-ingestive signals. It has been postulated that unpleasant symptoms after eating high-calorie fatty foods – referred to as dumping – may play a role in the alteration in food intake after RYGB surgery. Dumping is a frequent complication of bariatric surgery and is recognised as a set of symptoms that include nausea, indigestion, diarrhoea, and a sudden drop in blood pressure due to an extra amount of water that get to the blood from the small intestine. For most people, the symptoms improve over time and patients are advised to eat slowly, avoid sugary foods, and eat smaller, more frequent meals. One of the limitations of my study is that the patients were not asked about dumping, although, they were aware of it and had been given advice by the dietitian in the team. Further studies are needed to gain a better understanding of the effects of RYGB on macronutrient composition and how dumping would impact this matter.

3.8.3. Eating behaviour following RYGB

Monitoring the eating behaviour traits of individuals undergoing weight-loss interventions is crucial in determining their weight loss success. Candidates for bariatric surgery are found to have higher disinhibition and hunger ratings (431), however, this is not always the case when comparing surgical and non-surgical candidates (275).

3.8.3.1. *Dietary restraint and feelings of hunger following RYGB*

The concept of measuring restrained eating to assess eating behaviour, distinctive patterns of eating, eating disorders and weight loss success receives most of the attention in the literature, and was first introduced by Herman and Mack in 1975 (273). Dietary restraint refers to individual concerns about weight management and the methods used to manage body weight and restrict feeding, such as using smaller portions, avoiding fattening foods and stopping eating before reaching satiation to reduce food intake. Instead of relying on internal satiety signals to regulate energy intake, restraint eaters rely on a cognitive effort to limit food intake. Several commonly used eating behaviour instruments (DEBQ, TFEQ, and EDE-Q) were used in this study to capture post-RYGB dietary restraint. Although these instruments aim to identify participants who limit their food intake to prevent weight gain or promote weight loss, they capture different aspects of restrained eating and show conflicting results in weight control. The DEBQ and the TFEQ both measure successful attempts to restrict calorie intake (432), while the EDE-Q measures cognitively mediated attempts to eat less than the desired amount, whether successful or not. For more about these instruments see Chapter 2, Section 2.4.1 on Pages 65-74. The DEBQ-Restraint subscale can be subdivided into intentions to restrict food intake that accompany weight-loss attempts and actual behavioural restraint (types of positive restraint) that are associated less with emotional and externally induced eating (433). Meanwhile, the TFEQ-Restraint subscale can be subdivided into flexible and rigid control.

Flexible control means eating in moderation while controlling portion sizes, while more rigid control depends on the approach of eating either everything or nothing. The more flexible approach to restraint may protect individuals from disinhibited eating, while rigid restraint is based more on restraint theory that is often accompanied by dietary disinhibition where emotional or external cues act as triggers. The theory proposes that dietary restraint may induce counter-regulatory responses, lowering sensitivity to satiety signals and resulting in disinhibited binge-eating. There is no study comparing the results of the three available measures of dietary restraint that are used to measure eating behaviour or to predict weight loss (434). To my knowledge, there are also no previous studies examining the most appropriate restraint approach for RYGB candidates.

Evidence for the impact of dietary restraint on body weight is conflicting. Some evidence proposes that restraint is a protective factor against obesity, while others suggest that restraint is positively related to body weight and can be a risk factor relating to overeating and weight gain (435-439). Some evidence indicates that attempting to restrain oneself can lead to food cravings which can then be linked to higher disinhibition (uncontrolled eating and emotional eating), increasing the risk of greater weight gain and obesity in a community sample (440). It has also been found to increase the risk of obesity by up to four-fold (441). On the other hand, some evidence suggests that restraint is not always linked to energy intake regulation compensatory behaviours (442), and showed no impact on intake when portion size was changed (443) or on adherence to a dietary intervention (444). Restraint has been found to be low in women with obesity (445), or not related to body weight at all (446, 447). The mechanism underlying this discrepancy and why people with different restraint levels have different body weights still needs more extensive investigation. This can be clarified at least in part by the quality of diets and eating habits, such as whether the restraint that has been adopted is a flexible or rigid approach, what instruments have been used to identify restraint, and the

samples of participants that differed drastically across some studies (healthy college students to obese patients seeking weight-loss treatment). It might also depend upon the interaction between restraint and other traits such as disinhibition, hunger and external or emotional eating and the subsequent impact of this on body weight. Meanwhile, evidence from genetic studies suggests that restraint is associated differently with different BMI-increasing variants (436). Furthermore, parent-offspring eating behaviour dyads show that parental rigid restraint and disinhibition are linked to a higher offspring BMI (448), implying that family eating behaviour traits may be partially genetically determined.

Following surgery, one consistent finding is that disinhibition (uncontrolled eating or emotional eating) decreases, with either an increase in restraint (221, 249, 449, 450) or no change in restraint (451-453). This suggests that bariatric surgery may help people with some eating patterns (such as a high disinhibition) to improve their eating habits, resulting in greater weight loss. There is evidence that post-surgery improvements in eating habits are more strongly associated with weight loss success. Those who lose more weight postoperatively observed an increase in flexible restraint (454) and a decrease in disinhibition (uncontrolled and emotional eating) and hunger between one and ten years postoperatively (450). Eating behaviour patterns, therefore, play a significant role in weight loss performance after bariatric surgery, and participants who have an eating behaviour profile that supports body weight control are more likely to lose weight (455).

In the current study, the DEBQ showed that participants displayed a significant increase in restraint eating three months postoperatively, compared to their previous patterns. Although the level of restraint remains higher than the baseline one-year postoperatively, the difference had no statistical significance. No significant change in restrained eating was shown using other tools (the TFEQ or the EDE-Q). Differences in restraint results could be due to differences in the measuring process used to detect changes, which is perhaps more indicative of further

differences in the definition of restraint in each tool. The increase in restraint observed in the current study using DEBQ is in line with Pepino et al. (2014) who studied the impact of a 20% weight loss following bariatric surgery on eating behaviour associated with food addiction in a group of 44 women. They found a greater increase in restrained eating in the food addiction group compared to the non-food addiction group (269), which probably reflects the suggestion that different kinds of dieters can be identified through different restraint measures. Moreover, Neumann et al. (2018) used the DEBQ to study 440 participants who were categorized into successful and unsuccessful weight-loss maintenance participants, comparing them with members of the general population who have intentionally lost at least 10% of their maximum body-weight and have kept it off for at least a year over a two-year observation period. The study found that those who had successfully maintained weight loss scored significantly higher on the restrained eating subscales compared to the general population sample (270). A certain degree of restraint, therefore, seems to be necessary for successful weight-loss maintenance.

Scholtz et al. (2014) in their brain-imaging cross-sectional study, concluded that restrained eating measured by the EDE-Q was significantly lower in RYGB patients compared to gastric banding and control patients who had not undergone surgery. Differences between Scholtz's results and my study, which shows no change in EDE-Q restraint, may result from differences in study design based on a cross-sectional weight-loss dependent study vs a prospective surgical-duration dependent study (223). Moreover, the current finding showed no significant change in cognitive restraint measured by TFEQ, a previous study reporting an increase in cognitive restraint post-RYGB (221, 277). The reason for this discrepancy between my result and the literature could be due to the small sample size in my study (14 patients) compared with the following studies. Laurenius et al. (2012) studied eating behaviour in 43 participants longitudinally (six weeks, one and two years postoperatively) using the TFEQ, and reported an increase in cognitive restraint in the short-term (six weeks) after surgery. However, these

results were not maintained over the long-term period (one and two years) following RYGB (221). Similar results were obtained in the controlled longitudinal SOS study lasting for up to two years after obesity surgery compared with preoperatively among 487 surgical cases (277). In a case-control observational study aiming to compare eating behaviour in women living with obesity preoperatively and one-year after bariatric surgery, Hubert et al. (2019) were able to conclude that post-surgical patients had greater restraint and less hunger and disinhibition, measures using the TFEQ among 48 patients, than they had pre-operatively (276). It would be reasonable to hypothesize that low hunger levels with an increase in flexible restraint eating may protect against disinhibition and therefore obesity. Furthermore, people with lower levels of hunger and higher levels of cognitive restraint consumed fewer calories when averaged out across the year (456). Sarwer et al. (2008) performed a prospective investigation involving a larger number than this study (200 participants) and concluded that cognitive restraint three months postoperatively was associated with a higher percentage of weight loss two years after surgery. In addition, hunger and disinhibition significantly decreased from baseline to postoperative levels in their group, and high baseline dietary restraint was found to be an indicator of better adherence to the diet following RYGB (274). In contrast to Sarwer et al., Miras et al. (2015) conducted a prospective study of 90 patients to determine whether there were any differences in eating behaviour between bariatric surgery candidates and non-surgical weight loss treatments and to identify whether these behaviours can be used to predict weight loss after surgery. They found a negative correlation between higher baseline restraint and long-term weight loss (275). Unlike Sarwer's study, which looked at patients who had undergone RYGB only, Miras's study included RYGB, vertical sleeve gastrectomy and adjustable gastric banding patients. That may explain the discrepancy in the results as different surgery may have a different impact on restraint eating. Based on Polivy and Herman's restraint theory, higher levels of dietary restraint can lead to overeating and disinhibition, resulting in

higher consumption of calories after dieting (73, 273). However, some dieters can achieve sustained weight control by using self-regulation strategies such as restraint for controlling their weight and food intake (74, 261). Drawing definite conclusions about dietary restraint based on existing research is unwise, because existing research is limited, and the measurement of dietary restraint is inconsistent.

3.8.3.2. *Emotional and external eating following RYGB*

Emotional and external eating refers to eating in response to emotional or external food cues such as palatability were measured in this study using the DEBQ (278). People living with obesity compared to normal-weight individuals tend to be more prone to these behavioural traits, leading to overeating and obesity (457). These traits play crucial roles in analysing obesity and eating disturbances (74). Emotional eating was found to have a negative impact on excess weight loss two years after RYGB (458). In the current study there was a significant short-term reduction in external eating, but no change in emotional eating patterns during the study period. This is in contrast to patients following the RYGB procedure, who reported an early reduction in both emotional and external eating (269) that was maintained for up to two years after surgery (221). The level of emotional eating that the participants in the current study began with was low preoperatively, so perhaps there was little room for more improvement, which may explain the difference in my results compared with others in the literature.

Body shape concerns and dissatisfaction with body image can be defined as self-perception of weight, including intense fears of weight gain or disliking one's shape due to excess skin that might affect weight management. Body shape concerns can be also affected by body weight given the stigma surrounding obesity and being overweight (459). Being stigmatised is stressful and has a negative impact on general health (58, 59). Up to 71% of candidates for bariatric surgery experience concerns about body image and about 32% reported that shape weight concerns are two of the most common reasons for seeking surgery (460, 461). Shape

and weight concerns have also been associated with problematic health behaviour and mental health effects, such as disordered eating, depression, suicide risk, anxiety, poor health-related quality of life, low self-esteem, and sexual dysfunction (462-467). On average, following significant weight loss induced by bariatric surgery, patients experience improvements in concerns over shape and weight within the first few months after surgery, which may improve their quality of life, promote their psychological status, and improve weight-loss outcomes (465, 468-471). Moreover, a review of 45 cross-sectional, longitudinal and intervention studies reported general improvements in shape and weight concern up to two years post-bariatric surgery (468), which is in line with the growing evidence that suggests body image concerns are improved after weight loss (472-478). Consistent with previous research, this study found that reductions in weight and shape concerns measured by EDE-Q were associated with the reduction in body weight post-RYGB. However, some studies reported that some patients continue to experience concerns about excess skin, leading to subsequent body contouring procedures. Identifying patient characteristics such as weight concerns postoperatively may guide health care providers to provide specific interventions that target patients at risk of persistent body image dissatisfaction and improve surgery outcomes that could enhance weight loss outcomes and overall wellbeing.

3.8.3.3. *Disinhibition (uncontrolled eating) following RYGB*

A TFEQ instrument that measures disinhibition, cognitive restraint and hunger was used in the current study, and the result showed a significant reduction in disinhibition score three months postoperatively, which reduced even further at one-year compared to preoperative levels. Disinhibition is defined as a loss of control leading to overeating and eating opportunistically in response to external cues (479). Looking at this definition of disinhibition and the findings presented in the literature, the reduction in disinhibition shown in the current findings represents a favourable change that may support long-term weight loss success. Higher

disinhibition levels have been widely reported among people with obesity compared to normal-weight individuals (480, 481), and these levels are found to be associated in women with an increase in sweet food consumption during stressful times (482). However, Haynes et al. (2003) suggested that disinhibition may not work alone, and that its effect may interact with the level of the other TFEQ subscales (restraint and hunger) (483). For example, women with low restraint and high disinhibition scores consumed more food in conditions of no stress and reduced intake in response to stress compared with women with higher levels of restraint and higher disinhibition scores who ate more when under stress than they did in stress-free conditions (483), suggesting that the relationship between restraint and disinhibition eating influences eating in response to stress. In line with Haynes et al., Yeomans et al. (2004) reported similar findings in a study that looked at the impact of dietary restraint on short-term appetite in response to manipulated palatability, proving that women with a high level of restraint and a low level of disinhibition did not increase their food intake in response to palatability (484). Several studies have demonstrated the relationship between disinhibition and over-eating to food intake, and have concluded that low levels of disinhibition are related to lower food intake while higher disinhibition scores are associated with the consumption of less healthy food choices (high-fat foods and sweet foods) among women with obesity (485, 486) and higher levels of alcohol consumption in both genders (485-488). Alcohol not only contributes to excess weight and obesity but also to poorer general health. In a large-scale review that used both cross-sectional and longitudinal studies to explore the relationship between disinhibition and weight management, Bryant et al. (2008) concluded that disinhibition impacts individuals' food intake and food choice, as well as weight management and eating behaviour (256). Reduction in disinhibition is one of the critical eating behaviour changes, and may lead to successful long-term maintenance of weight loss for up to 10 years (489). Bariatric surgery results in a decrease in disinhibition and improved eating behaviour,

leading to weight loss (277). Like the current findings, the SOS study reported a reduction in disinhibition up to 2 years after obesity surgery, which is in line with other recently published case-control studies in women one-year after RYGB or sleeve gastrectomy using the same measuring tools (276). In their longitudinal study, Laurenius et al. (2012) showed an early reduction in disinhibition after RYGB in both genders that lasted up to 2-years postoperatively (221). There is some controversy surrounding the use of disinhibition as a predictor for weight loss after surgery. Using baseline scores to predict post-surgery weight loss success is generally limited, and evidence indicates that baseline restraint has a negative effect on post-surgical weight loss, while baseline disinhibition has a positive impact on weight reduction (275, 490).

Miras et al. (2015) looked at weight loss prediction based on disinhibition in a prospective study of 90 patients who underwent RYGB, sleeve gastrectomy or gastric banding compared with 36 patients who underwent pharmacotherapy or lifestyle interventions and found a positive correlation between the percentage of weight lost one-year postoperatively and preoperative levels of disinhibition (275), suggesting that disinhibition behaviour might prevent weight loss and that might be addressed postoperatively. However, Leibbrand and Fichter (2002) measured variables predicting overall weight loss at the 18-month follow-up among 109 individuals who underwent 10 weekly sessions of cognitive behavioural treatment programmes followed by a maintenance program, compared with participants who followed the usual obesity programme (491). Disinhibition of the TFEQ in their study did not predict weight loss after the intervention, in contrast to Miras et al.'s findings. This discrepancy may be due to the difference in treatments used: behavioural in the case of Leibbrand and Fichter, vs surgical for Miras et al. The latter group's findings are more comparable to the current study, which involved the physiological manipulation of gut hormone levels, which may mediate changes in eating behaviour through different mechanisms. RYGB could therefore be considered a suitable treatment for patients with disturbances in eating behaviour – such as

disinhibition – and such patients could benefit from these alterations in eating behaviour postoperatively.

3.8.4. Psychological status following RYGB

Obesity is not only affected by eating behaviour, but also by psychological traits such as impulsivity, depression, and anxiety. The following section explores the impact of RYGB on these psychological states at three-month and one-year post-RYGB.

3.8.4.1. *Impulsivity, depression, and anxiety following RYGB*

The current findings showed no significant changes in impulsivity, reward sensitivity (reward responsiveness, reward drive, hedonic or behavioural inhibition), or in levels of depression and anxiety as measured by the Barratt Impulsiveness Scale, the Behavioural Activation, and Inhibition Scale (BAS/BIS) or the Beck Depression Inventory-II and the Hospital Anxiety and Depression Scale (HADS). Many of these traits are considered common among patients with obesity (491), and to have an impact on eating behaviour and contribute to limited weight loss after bariatric surgery. At a behavioural level, impulsive people, i.e. those who are unable to resist an immediate reward instead of waiting for a more significant longer-term reward (492), are more likely to eat high-calorie foods (493). Reviews show that patients with obesity – particularly those who seek bariatric surgery – tend to show higher levels of impulsivity and associated neurological problems (494-496). This was in line with previous findings that reported depression (491) and impulsivity (497) as common problems among people who live with obesity. Symptoms of depression were found to improve when weight loss was achieved (277, 498, 499). The discrepancy between the current results and the literature is most likely due to the minimal scores in impulsivity and depression before the surgery and throughout the trial period, which contrasts with previous reports. It may also be due to the current study being underpowered due to being powered for the clinical endpoints of glycaemia and weight loss.

3.8.5. Health-related quality of life following RYGB

The current study showed a general improvement in quality of life, a finding that is in line with previous studies that showed consistent improvements in weight-related and general health-related quality of life after bariatric surgery as measured by IWQOL and SF-36 respectively (500). Studies showed that HR-QoL is generally lower in individuals with obesity who seek treatment than in those who do not (344, 501). Obesity is associated with significant physical impairment, joint pain, and poor quality of life. However, in the current findings, a significant long-term improvement in the generic HR-QoL could be seen in terms of pain as well as physical and emotional function up to one-year postoperatively, which is in line with King et al. (2016), who reported a 50-70% improvement in these domains up to 3 years post-RYGB (502). The most significant impairments in health-related quality of life were related to pain (503) and to physical functionality. In the current study, there were improvements in these two domains as well as an improvement in the participants' sexual lives post-RYGB. Improvements in HR-QoL post-RYGB could be expected due to a reduction in excess bodyweight and obesity-specific symptoms.

3.8.6. Alcohol consumption following RYGB

Studies have shown that blood alcohol levels peak higher and faster after RYGB surgery, which tends to make patients more sensitive to alcohol than they were before RYGB. That could be due to postoperative alterations in metabolism that contribute to the more rapid absorption of alcohol into the bloodstream as it takes less time to reach the small intestine, where it is absorbed. As well as the obesity-related or substance-addiction differences in brain reward that have been observed using evidence from fMRI studies supported by eating behaviour questionnaires (504), the RYGB-related alteration in brain reward may also impact alcohol consumption. Moreover, some patients with obesity tend to consume food to deal with anxiety

or stress as a coping mechanism. However, postoperatively their ability to consume a large amount of food is reduced. They may therefore develop new strategies to cope with stress such as using alcohol instead of food to cope with stressful situations or negative emotions. There is evidence suggesting the development and increase in alcohol use disorder (AUD) among RYGB patients (505) including those without previous histories of AUD before surgery (376, 506) or without a history of alcohol consumption before surgery (377). Additionally, the risk of developing an AUD was found to be doubled for RYGB patients compared with other bariatric procedures, possibly due to altered alcohol metabolism after RYGB (507).

In the current study, the prevalence of alcohol consumption measured using the AUDIT was low at baseline and remained low at three months and one-year post-surgery. Data from several studies suggest that alcohol consumption decreases during the first year postoperatively (505, 506, 508-511). Other studies have reported that 40-50% of individuals who had high-risk alcohol use before surgery are more likely to discontinue high-risk drinking within the first year after RYGB (376, 512, 513). That could be due to medical advice given to patients before the operation to abstain from alcohol during the first three-month post-surgery. However, another possible explanation of unchanged alcohol consumption post-RYGB is in the timing of the questionnaires, which were given to measure the intake up to one-year post-surgery, which may be early for patients to develop alcohol disorders. Moreover, the current group was predominantly female (85.7%) and in a recent review in alcohol intake after RYGB, Briegleb and Hanak (2020) identified being male and undergoing an RYGB as one of the risk factors in developing an AUD (514). Long term follow-up after the second year following the operation, is needed to give a better understanding of the mechanisms that underlie the development of AUD.

3.9. Conclusion of RYGB study

In summary, patients living with obesity showed favourable changes in behavioural eating post-RYGB compared with pre-operatively, including the reduction in reward eating, disinhibition and external eating, weight and shape concerns and an increase in behavioural restraint. Some of these changes were sustained for up to one-year post-RYGB, and this appears to be critical for successful long-term weight loss maintenance. Such changes might be generally attributed to weight loss and the reduction in the food intake achieved post-operatively, not just the anatomical restriction of the gut.

3.10. Limitations

This study has limitations. Firstly, the main drawback of the questionnaires used was the fact that they are based on self-reporting. No individual follow-up interviews were undertaken, and no other observations were made. Secondly, the length of the questionnaires and the time required to complete them may have affected the accuracy and the reliability of the results. Thirdly, the limitation involved the use of food diaries to assess calories and macronutrient intake. Although this is a frequently used approach in many studies, the underreporting of caloric intake is a significant problem in obesity studies (515, 516). Using food diaries in dietary assessment is a significant limitation when following up on RYGB patients, as it is prone to selection bias and may not work as a direct assessment of measuring energy intake and food preferences (517, 518). This may explain the result of intake at baseline levels in the current study for the surgical patients who reported consuming around 1880 kcal/day, which is physiologically impossible for a person with a BMI of 40kg/m^2. By comparing self-reported food diaries to the doubly-labelled water method in some studies, inaccuracies in self-reported consumption at the individual level were identified, with the greatest bias was observed in population with obesity (−35 and −50%) compared to lean and nonathletic groups (0 to −20%) (519). They found that most disparities were attributable to underreporting, although some

subjects lost weight over the reporting period, implying that some of the disparity was due to under-eating. Participants may report their intake inaccurately or incompletely and/or may alter their usual eating patterns during the period of assessment. To limit these sources of error, food intake data should be examined critically for individual bias in reporting and researchers should look at how this could influence the conclusions drawn using the Goldberg equation (520). However, that is not sufficient to eliminate the biases from this type of obesity-related selective reporting errors.

Other alternative food intake methods such as the biomarkers of intake, including urinary nitrogen excretion and doubly labelled water measures of energy expenditure might be expensive, but are a potentially valuable source of accuracy. Fourthly, this study may be underpowered in terms of detecting changes in variables of interest due to the small sample size (N=14) at baseline and the fact that three (21%) of these fourteen enrolled participants were lost to follow-up. The number of participants in the study is small, although comparable with some similar studies that have used these questionnaires to examine the changes in eating behaviour (221, 262, 268, 270), reward drive to eat (294, 383, 384), psychological status (271), and health-related quality of life (354, 359, 362), and with those examining change in taste post-bariatric surgery (232, 243, 261, 269, 385, 386) using the same tools as these been used in my study. The calculation of the study was based on a 30% reduction in food intake. This was the main outcome for the main study that my study forms a part of. It suggested that ten participants per group would be adequate to give a power of 80%. Therefore, my current study can provide a basis for planning an extension of this study using larger numbers of participants (see Chapter7, Section 7.4 on Pages 263-265). Patients lost to follow-up often have a different prognosis than those who complete the study. However, there were no material differences between participants who adhered to the programme and those lost to follow-up at baseline in all the variables of interest. The common reason for the loss of follow-up among these three

participants included issues such moving out of the study area, finances, and work commitments. The pilot results seen in this study provide a basis for planning the extension of this study with larger numbers (see Chapter 7, Section 7.4 on Page 262-264). Fifthly, the study sample is predominantly female. Although this unequal gender distribution in bariatric surgery patients might impact the measured factors in this study, it is consistent with the figure seen in the literature, where women account for 80% of individuals who undergo bariatric surgery (521, 522) despite comparable obesity prevalence across genders.

To add a new aspect to this study and explore the previous findings in greater length, the next chapter will explore changes in the same parameters that were measured in this chapter on people living with obesity and T2DM, but after following the very-low-calorie diet. The findings will be then compared to the RYGB results.

4. CHAPTER FOUR:

VERY-LOW-CALORIE DIET

4.1. Introduction

According to current guidelines, lifestyle modifications focused on changing eating habits by reducing calorie intake and increasing physical activity are considered first-line management strategies for obesity and T2DM when a substantial weight loss is needed (523-525). Dietary interventions using meal replacement strategies, including VLCDs containing fewer than 800 kcal/day, facilitate greater short-term weight losses than other dietary interventions, with the potential remission of Type 2 diabetes and fewer complications in comparison to bariatric procedures (526). Evidence from the Look AHEAD study, the biggest randomised controlled trial using strategies to reduce calories by offering up to two meal replacements per day (intensively managed through a VLCD) has shown that intensive lifestyle interventions resulted in a weight loss of 5% or more that was sustained for up to 8 years in comparison with a 3.5% weight loss in the control group receiving the usual form of care (Diabetes Support and Education) (113). A modest weight loss of only 5% is clinically meaningful in that it positively impacts biomarkers of glucose control and provides long-term health benefits (527). The systematic evaluation of evidence shows that meal replacement interventions lead to greater weight loss (528) and greater levels of adherence (529, 530) compared with receiving traditional food. Such methods are also more likely to ensure an adequate intake of essential nutrients (530, 531), while demonstrating higher satisfaction levels and lower drop-out rates compared to other diets (528, 529, 531, 532). Evidence suggests that the risk of developing T2DM after a substantial weight loss is reduced even if the weight was regained (533). The remission of T2DM for at least 2 years was also observed in 9.2% of the participants in the Look AHEAD study (534). Recently published findings from the DiRECT study suggest that the remission of T2DM – although remission is not defined according to ADA criteria – can be achieved using a VLCD weight management intervention (115). This intervention included stopping anti-diabetic drugs and a total VLCD diet replacement for 12–20 weeks, followed by

2–8 weeks of food reintroduction and then a programme of structured support for weight-loss maintenance. At 1 year, 24% of the participants had achieved a weight loss of at least 15 kg, with 86% of participants also achieving diabetes remission. More than a third of the intervention group maintained at least a 10 kg weight loss as well as sustained diabetes remission after 2 years (115).

As well as the effect of meal replacements on weight loss and diabetes remission, studies have found that VLCDs help reduce food cravings. Overweight individuals or those with obesity tend to have higher levels of cravings and desire to consume certain types of calorie-dense food than lean individuals, which is believed to contribute to difficulty in sustaining healthy lifestyle behaviour (535). Several behavioural studies have shown that extended calorie restriction is also considered to be associated with a reduction in cravings and improved dietary restraint, further supporting the idea that changes in cravings for certain foods and dietary restraint may represent changes in reactivity to food cues in the brain (536-540). For example, Martin et al. (2006) used the Food Craving Inventory to measure food cravings over an 11-week and found that food cravings were significantly diminished during the course of a VLCD (536). A meal replacement diet such as a VLCD may restrict variety, promoting a lower intake (541) by eliminating choice and controlling portion size (542-544), helping to reduce food cravings. Such decreases in food craving associated with energy restriction were recently proved to coincide with increased personal control over ingestion and food cravings through the examination of fMRI food-cue reactivity in the human brain (543).

Overall, VLCDs are effective for weight loss, diabetes remission and reducing food cravings. However, to the best of my knowledge, no study compares VLCD intervention with RYGB in a behavioural sense. This study aimed to examine the effects of a VLCD on eating behaviour, psychological status, and food reward and health-related quality of life in comparison to RYGB among patients with obesity and T2DM using a range of different questionnaires.

4.2. Research aim

To investigate the efficacy of a VLCD on eating behaviour, food reward, psychological status, quality of life and post-intervention food intake in people with obesity and T2DM in comparison to RYGB.

4.3. Research hypotheses

1. That VLCDs bring about favourable changes in eating behaviour and psychological wellbeing as observed post-RYGB.
2. That VLCDs decrease the reward drive to consume highly palatable food, as observed three months post-RYGB.
3. That improved eating behaviour, psychological health, and reduction in the reward drive to consume highly palatable food is sustained 8-weeks after VLCD.

4.4. Methodology

This VLCD study was designed as a prospective interventional study to investigating the effects of diet-induced weight loss on weight and eating behaviour, reward drive and psychological status after one-month on a VLCD and two-month after finishing it. The results will then be compared to the RYGB group population (discussed in the previous chapter) as a reference group for the study.

4.5. Study protocol

Study visits were conducted at the Clinical Research Facility (CRF) by the study team. Participants were asked to fast for at least 10 hours and to abstain from alcohol for 24 hours prior to each visit. Participants were asked to follow a complete meal replacement plan, a diet of 800 Kcal/day for 4 weeks based on the Cambridge Weight Plan consisting of soups, shakes and bars. The Cambridge Weight Plan (254) is one of several very-low-calorie diets currently available to support rapid weight loss. One of the reasons for choosing the Cambridge diet is that it was designed to preserve lean body mass by providing varying amounts of high-quality protein and carbohydrates and fulfilling all daily nutritional requirements. The diet has also been used widely by similar studies (114, 115). Participants were instructed to only consume the diet products and to keep themselves well hydrated and were seen on a weekly basis by the study dietitian to review progress and address any problems arising from the diet until the plan was finished. After one-month on the VLCD, the first examination of the changes in participants' eating behaviour and dietary intake took place. Anthropometric measurements were taken at each visit, including body weight, waist circumference and bioelectrical impedance analysis. See Figure 4, Chapter 2 on Page 85 for the study visit plan and full information about study methodology, data collection and preparation.

The VLCD results were then compared with the RYGB results (see Chapter 2, Section 2.3.1 on Page 60 for more details about the RYGB study) The same factors of interest were measured for the RYGB group as the VLCD group, using different follow-up intervals (at baseline and three months post-RYGB compared with baseline and one-month on VLCD). There are two reasons for the differences in the measured time in the RYGB group in comparison to the VLCD group. Firstly, when the study was first designed, and based on the literature available at the time, RYGB weight loss after three months matched the one-month weight loss using VLCD, and secondly to reduce the confounding effects of an initial liquid diet regime or the physical effects from surgery. For more details see Chapter 2, Section 2.3.2 on Page 61.

4.5.1. Questionnaire data

The following questionnaires were completed before the operation and were repeated three months and one-year postoperatively. For more details see Chapter 2, Section 2.4.1 on Pages 65-74.

4.5.1.1. Eating and behaviour questionnaires

3.4.1.1.12 *Dutch Eating Behaviour Questionnaire (DEBQ)* (70) to assess restraint, emotional, and external eating. A higher score indicates a greater tendency towards a measured response.

3.4.1.1.13 *Three-Factor Eating Questionnaire* (272) to measure restraint, disinhibition and hunger. Higher scores indicate higher levels of measured response.

3.4.1.1.14 *Eating Disorder Examination Questionnaire* (278) to assess the psychopathology of eating-disorder behaviour. Higher scores indicate higher levels of measured response.

4.5.1.2. Reward drive to eat

3.4.1.1.15 *Power of Food Scale* (287) to measure the hedonic drive to eat more palatable food, rather than the actual consumption of palatable foods. A higher score reflects the degree of control or power food has over an individual.

4.5.1.3. Psychological questionnaires

3.4.1.1.16 The Beck Depression Inventory (BDI-II) (295) to measure the presence and severity of depression and anxiety. Cut-off scores used were: 0–13 (minimal depression), 14–19 (mild depression), 20–28 (moderate depression) and 29–63 (severe depression).

3.4.1.1.17 *Behavioural Inhibition and Activation System (BIS/BAS) scales* (301) to measure sensitivity to punishment and reward.

3.4.1.1.18 *Hospital Anxiety and Depression Scale (HADS)* (309) to measure symptoms of depression and anxiety levels in general hospital patients. Cut-off scores are: 0-7 (normal); 8-10 (borderline abnormal) and 11-21 (abnormal) (310).

3.4.1.1.19 *Barratt Impulsivity Scale* (323) to measure impulsiveness. A higher score represents a higher rate of impulsivity.

4.5.1.4. Health-related quality of life

3.4.1.1.20 *Health-related Quality of Questionnaire* (369) to assess the impact of obesity on quality of life. Scores range from 0-155, with higher scores indicating a poorer quality of life.

3.4.1.1.21 *Short-Form 36 Health Survey Questionnaire (SF36)* (346) to evaluate generic health-related quality of life across eight domains: physical functionality, role limitations due to physical problems, vitality, bodily pain, social functionality, role

limitations due to emotional problems, mental health and general health perceptions. Scores range from 0-100, with higher scores indicating better health status.

4.5.1.5. Behavioural changes

3.4.1.1.22 *Alcohol Use Disorders Identification Test* (AUDIT) (372) to assess alcohol use and alcohol-related consequences.

4.5.2. Food intake data

Each participant was given a food diary with detailed written instructions to record all food and drink consumed over four days – preferably two weekdays and two weekend days. Participants were asked to provide details of cooking methods, brand names and portion sizes. See Chapter 2, Section 2.4.2 on Page 75 for more information about food intake data collection and preparation.

4.5.3. Statistical analysis

Within the group comparison of averages (the time effect of the VLCD) for each parameter at baseline, one-month and three-month was made by fitting a mixed-effects model (overall P-value) and correcting for multiple comparisons using Bonferroni's post hoc test (adjusted P-value). According to the normality result, parametrical or non-parametrical tests were performed. For between-group comparisons (VLCD vs RYGB) the mean change in scores from baseline values were calculated as before intervention scores minus after/follow-up intervention scores for each parameter and each subject in each group intervention, and then analysed using an unpaired t-test to compare the differences between RYGB and VLCD). All statistical analyses were performed, and all figures were generated using GraphPad Prism 9 (GraphPad Software, San Diego, CA). See Chapter 2, section 2.5 for more information about statistical analysis.

4.6. Results

4.6.1. Participant characteristics for VLCD questionnaire data

A total of 24 participants were recruited for the VLCD study. Ten were excluded from the questionnaire analysis for the following reasons:

- One participant developed a flare-up of Rheumatoid Arthritis prior to starting the diet
- Two could not adhere to the diet and did not complete 28 days of the VLCD
- One participant changed his mind prior to the start of the diet but after having completed a baseline study visit.
- Six failed to complete the questionnaires

This meant that questionnaire data were available for fourteen of the participants at baseline and eight at the follow-up period. See Figure 5, chapter 2 on page 86, for the consort diagram of patient entry into studies.

The baseline characteristics for the study groups are shown in (Table 8 on page 139). As in the RYGB group, the VLCD group was predominantly female (64%), with a mean BMI of 39.9 kg/m^2. Fifty-seven per cent of the patients were diabetic, and the rest were prediabetic. None of the VLCD group was on any antidepressant treatment.

Table 8: *Baseline characteristics of studied participants (VLCD/RYGB)*

	VLCD N=14	**RYGB N=14**
Gender (F:M)	(9:5)	(12:2)
Age (years)	49.1±2.9	46.9±3.2
Weight (kg)	109.7±5.7	116.6±6.9
BMI (kg/m^2)	39.9±1.2	42.4+1.6
Waist (cm)	126.2±4.3	121.9±3.2
Hip (cm)	126.1±3.7	133.4±4.5
Waist: Hip Ratio	1±0.02	0.9±0.03
Neck (cm)	42±1.4	41±1
FM (%)	41.9±2.3	46.6±1
T2DM, n (%)	8 (57)	11 (79)
Prediabetic, n (%)	6 (43)	3 (21)
Treatment, n (%)		
▪ **Diet only**	7 (50)	5 (36)
▪ **Metformin only**	7 (50)	9 (64)
On antidepressant treatment, n (%)	0 (0)	2 (14)
Systolic blood pressure (mmHg)	129.0±3	133.1±4
Diastolic blood pressure (mmHg)	76.59±3.1	74±4
Heart rate (beats per min)	76.95±3.1	76±2.9
HbA1c (mmol/mol) (Not normal)	54.27±3.8	57.5±3.8
Fructosamine (µmol/l)	255.1±12	252.9±10

Data presented as mean±SEM or median [interquartile range] for parameters do not display Gaussian distribution. A Fisher exact test was used for categorical data. Prediabetic includes impaired glucose tolerance, impaired fasting glucose, or HbA1c of 6.0–6.4% (42–48 mmol/mol). Abbreviations: BMI, Body mass index; RYGB, Roux-en-Y Gastric Bypass; VLCD, Very-Low calorie Diet; T2DM, Type 2 diabetes mellitus; FM, Fat mass; HbA1c, Glycated Haemoglobin

4.6.2. Eating behaviour following VLCD

For the VLCD group, eating behaviour questionnaires indicated that one-month on the VLCD did not modify eating behaviour or psychological status compared to pre-VLCD levels using the mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test. The only statistically significant change that was observed after VLCD compared to before was in dietary restraint, measured by the EDE-Q. There was a statistically significant increase in dietary restraint after one-month on the VLCD (P=0.0003) that remained non-significantly higher than the baseline two-month after the VLCD. In comparison to the RYGB, external eating measured by TFEQ, restraint measured by DEBQ, and reward drive to eat measured by PFS were significantly lower three months post-RYGB compared to one-month on the VLCD (Table 9 on Page 143).

4.6.2.1. *The Dutch Eating Behaviour Questionnaire (DEBQ) following VLCD*

Within the VLCD group, no significant difference was found at any time-point measured across all the three DEBQ subscales (dietary restraint, external or emotional eating) measured using a mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test. However, a between-group comparison (VLCD vs RYGB) at the first time-point identified a significant reduction in the change from baseline in the DEBQ-External eating at three months post-RYGB compared with one-month on the VLCD using the unpaired t-test (P=0.0018) (Table 9 on Page 143).

4.6.2.2. *Three-Factor Eating Questionnaire (TFEQ) following VLCD*

No significant difference was identified in the VLCD group at any time-point across all three domains of TFEQ (cognitive-restraint, disinhibition, and hunger). In the between-group comparison, the RYGB group showed a significant reduction in cognitive restraint measured by comparing the change from baseline between the groups using unpaired t-tests three months

post-RYGB vs one-month on the VLCD, and that reduction remained significant and showed a greater reduction at the second time-point (P=0.01 at both time-points) compared to the VLCD group. There were no statistically significant differences in hunger or disinhibition subscales in between-group comparisons at any time-point (Table 9 on Page 143).

4.6.2.3. *Eating Disorder Examination Questionnaire (EDE-Q) following VLCD*

There was a statistically significant increase in EDE-restraint after one-month on the VLCD (P=0.0007), and this increase remained significant two-month after the VLCD (P=0.0003). There were no significant changes at any time-point across all other domains of the EDE-Q (weight concerns, shape concerns, eating concerns and global score). No significant difference was identified in any domains in between-group comparison at any time-point (Table 9 on Page 143).

4.6.3. Food reward following VLCD

4.6.3.1. *Power of Food Scale (PFS) following VLCD*

No significant differences were identified in the PFS within the VLCD group at any time-point. For between-group comparisons, RYGB at three months showed a significant reduction in reward response to food, according to the PFS compared with the VLCD at one-month (P=0.005). This difference remained significant for up to a year post-RYGB when compared to two-month after the VLCD (second time-point) (P=0.004) (Table 9 on Page 143).

4.6.4. Psychological and behavioural questionnaires following VLCD

Other psychological and alcohol intake outcomes, including the following scales, showed no significant changes in any of the variables measured at one-month and two-month post-VLCD.

- Impulsivity, measured by *Barratt Impulsiveness Scale (Barratt)*
- Punishment and reward sensitivity, measured by the *Behavioural Inhibition System/Behavioural Activation System (BIS/BAS) Scales*
- Depression symptoms over the last 2 weeks, measured by *Beck Depression Inventory (BDI-II)*
- Anxiety and depression, measured using *Hospital Anxiety and Depression Scale*
- Alcohol intake, measured by *Alcohol Use Disorders Identification (AUDIT)* (Table 10 on Page 146).

Table 9: *Eating behaviour and food reward following VLCD/RYGB*

Variables	**VLCD**	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**RYGB**	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**VLCD vs. RYGB** *P-value* [c]
Eating Behaviour Questionnaire							
The Dutch Eating Behaviour Questionnaire (DEBQ)							
Dietary restraint (score/5)							
Baseline (*n*)	2.7±0.18 (*14*)	0.82	>0.99	2.67±0.16 (*14*)	0.007 **	0.20	
After treatment (*n*)	3.06±0.3 (*11*)	(-1.16 to 0.49)	(-1.43 to 1.26)	3.48±0.26 (*13*)	(-1.45 to -0.16)	(-1.52 to 0.59)	
Δ from baseline^	**+0.38**			**+0.75**			**0.34^**
Follow-up (*n*)	2.81±0.41 (*8*)			3.14±0.43 (*11*)			
Δ from baseline#	**+0.08**			**+0.53**			**0.47#**
Emotional eating (score/5)							
Baseline (*n*)	2.73±0.24 (*14*)	0.18	0.21	2.5±0.27 (*14*)	0.109	0.56	
After treatment (*n*)	2.27±0.35 (*11*)	(-0.85 to 0.18)	(-4.36 to 0.10)	2.15±0.25 (*13*)	(-0.27 to 1.24)	(-1.10 to 1.14)	
Δ from baseline^	**-0.27**			**-0.37**			**0.76^**
Follow-up (*n*)	3.17±0.35 (*8*)			2.51±0.46 (*11*)			
Δ from baseline#	**+0.17**			**+0.18**			**0.98#**
External eating (score/5)							
Baseline (*n*)	3.04±0.17 (*14*)	0.56	>0.99	3.26±0.18 (*14*)	0.002 **	0.07	
After treatment (*n*)	2.82±0.22 (*11*)	(-0.22 to 0.66)	(-0.72 to 0.79)	2.29±0.24 (*13*)	(0.31 to 1.65)	(-0.14 to 1.85)	
Δ from baseline^	**-0.17**			**-0.95**			**0.01^***
Follow-up (*n*)	3.00±0.29 (*8*)			2.41±0.34 (*11*)			
Δ from baseline#	**-0.04**			**-0.72**			**0.38#**
Three-Factor Eating Questionnaire (TFEQ)							
Cognitive Restraint (score/21)							
Baseline (*n*)	8.43±1.40 (*14*)	>0.99	0.15	10.29±1.4 (*14*)	0.11	0.12	
After treatment (*n*)	9.09±1.43 (*11*)	(-3.52 to 2.19)	(-10.07 to 1.43)	6.08±1.29 (*13*)	(-0.79 to 9.21)	(-1.23 to 11.58)	
Δ from baseline^	**+1.8**			**-3.9**			**0.01^***
Follow-up (*n*)	12.75±1.73 (*8*)			5.11±1.62 (*11*)			
Δ from baseline#	**+3.37**			**-4.89**			**0.01#***

			Disinhibition (score/16)				
Baseline (*n*)	8.71±0.85 (*14*)	0.61	>0.99	8.78±0.68 (*14*)	0.002**	0.013*	
After treatment (*n*)	7.64±1.22 (*11*)	(-1.94 to 3.35)	(-2.31 to 3.74)	6.23±0.57 (*13*)	(0.84 to 4.27)	(0.70 to 5.98)	
Δ from baseline^	**-0.9**			**-2.385**			**0.16^**
Follow-up (*n*)	8.00±0.91 (*8*)			5.44±0.96 (*11*)			
Δ from baseline#	**-0.75**			**-3.00**			**0.84#**
			Hunger (score/14)				
Baseline (*n*)	7.21±0.94 (*14*)	>0.99	>0.99	6.36±0.75 (*14*)	0.42	0.21	
After treatment (*n*)	6.82±1.17 (*11*)	(-2.38 to 3.17)	(-5.71 to 6.26)	7.31±0.61 (*13*)	(-3.26 to 1.36)	(-2.77 to 1.93)	
Δ from baseline^	**-0.64**			**+0.69**			**0.32^**
Follow-up (*n*)	8.38±0.80 (*8*)			6.78±0.57 (*11*)			
Δ from baseline#	**+0.75**			**+0.42**			**0.84#**
			Eating Disorder Examination Questionnaire (EDEQ)				
			Restraint Eating (score/6)				
Baseline (*n*)	1.31±0.33 (*14*)	0.0003 ***	0.68	1.44±0.33 (*14*)	0.26	0.367	
After treatment (*n*)	3.71±0.34 (*11*)	(-3.48 to -1.31)	(-2.63 to 1.06)	2.32±0.52 (*13*)	(-2.69 to 0.92)	(-2.32 to 1.25)	
Δ from baseline^	**+2.42**			**+0.76**			**0.054^**
Follow-up (*n*)	2.10±0.67 (*8*)			1.98±0.60 (*11*)			
Δ from baseline#	**+0.79**			**+0.62**			**0.99#**
			Weight Concern (score/6)				
Baseline (*n*)	2.79±0.28 (*14*)	0.99	>0.99	3.40±0.38 (*14*)	0.035*	0.048*	
After treatment (*n*)	2.55±0.25 (*11*)	(-0.45 to 0.95)	(-1.52 to 1.91)	2.52±0.35 (*13*)	(0.09 to 1.97)	(0.19 to 3.16)	
Δ from baseline^	**-0.24**			**-0.88**			**0.20^**
Follow-up (*n*)	2.60±0.50 (*8*)			1.76±0.42 (*11*)			
Δ from baseline#	**-0.19**			**-1.64**			**0.29#**
			Eating Concern (score/6)				
Baseline (*n*)	0.69±0.28	0.55	0.57	1.45±0.44 (*14*)	0.314	0.312	
After treatment (*n*)	1.23±0.47	(-1.63 to 0.55)	(-0.92 to 0.34)	0.85±0.28 (*13*)	(-0.99 to 2.18)	(-0.87 to 2.53)	
Δ from baseline^	**+0.45**			**-0.70**			**0.12^**
Follow-up (*n*)	0.98±0.30			0.62±0.43 (*11*)			
Δ from baseline#	**+0.09**			**-0.61**			**0.32#**

			Shape Concern (score/6)				
Baseline (*n*)	3.25±0.37	0.29	>0.99	3.89±0.40 (*14*)	0.22	0.096	
After treatment (*n*)	2.71±0.29	(-0.31 to 1.39)	(-1.89 to 2.37)	3.01±0.47 (*13*)	(-0.37 to 2.14)	(0.06 to 1.98)	
Δ from baseline^	**-0.62**			**-0.99**			
Follow-up (*n*)	3.01±0.66			2.05±0.53 (*11*)			**0.52^**
Δ from baseline#	**-0.19**			**-1.2**			**0.32#**
			Global (score/6)				
Baseline (*n*)	2.01±0.26	0.09	>0.99	2.5±0.37 (*14*)	0.290	0.186	
After treatment (*n*)	2.54±0.27	(-1.14 to 0.08)	(-1.52 to 1.21)	2.18±0.33 (*13*)	(-0.72 to 1.40)	(-0.27 to 2.13)	
Δ from baseline^	**+0.48**			**-0.43**			**0.07^**
Follow-up (*n*)	2.16±0.47			1.59±0.40 (*11*)			
Δ from baseline#	**+0.038**			**-0.91**			**0.33#**
			Food Reward Questionnaire				
			Power of Food(score/5)				
Baseline (*n*)	2.69±0.28	0.59	0.16	3.18±0.29 (*14*)	0.0009***	0.005 **	
After treatment (*n*)	2.50±0.30	(-0.20 to 0.57)	(-2.36 to 0.36)	2.04±0.29 (*13*)	(0.47 to 1.81)	(0.31 to 2.31)	**0.005^****
Δ from baseline^	**-0.15**			**-1.08**			
Follow-up (*n*)	3.69±0.33			1.87±0.26 (*11*)			**0.004#****
Δ from baseline#	**+0.58**			**-1.34**			

Data are displayed as mean±SEM (95% CI). The scores are based on set of questionnaires for VLCD and RYGB at different time points**. 1-For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group at different time point performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value***[a], before treatment vs after treatment; ***P-value***[b], before treatment vs at follow-up). **2- For between groups comparisons** (VLCD vs RYGB) of the averages of the changes from baseline; **Δ from baseline^** change from baseline at one-month on VLCD or at three months post-RYGB**; Δ from baseline#**, change from baseline at follow-up (at two-month post VLCD) or (at one-year after RYGB); ***P-value***[c] = difference in changes in treatment effect from baseline between groups (VLCD vs RYGB) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for VLCD) vs (Δ from baseline^ for RYGB) and # refer to the *P-value* of (Δ from baseline# for VLCD) vs (Δ from baseline# for RYGB); Abbreviation: VLCD, Very-Low Calorie Diet; RYGB, Roux-en-Y Gastric Bypass. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

Table 10: *Psychological and behavioural status following VLCD/RYGB*

Variables	**VLCD**	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**RYGB**	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**VLCD vs. RYGB** *P-value* [c]
<u>Psychological status Questionnaires</u>							
Barratt Impulsiveness (score/120)							
Baseline (*n*)	66±4.14 (*14*)	0.10	0.09	60.86±3.07 (*14*)	>0.999	>0.999	
After treatment (*n*)	59.82±4.72 (*11*)	(-1.04 to 13.40)	(-0.92 to	62.54±2.59 (*13*)	(-9.43 to	(-10.88 to 8.39)	
Δ from baseline^	**-5.63**		11.92)	**+1.69**	6.07)		**0.07^**
Follow-up (*n*)	60.50±5.06 (*8*)			62.86±2.7 (*11*)			
Δ from baseline#*	**-7.37**			**+2.0**			**0.05#**
Behavioural Inhibition System/Behavioural Activation System (BIS/BAS) Scales							
Drive Seeking (score/16)							
Baseline (*n*)	10.00±0.59 (*14*)	0.96	0.10	11±0.67 (*14*)	0.16	0.36	
After treatment (*n*)	9.27±0.99 (*11*)	(-1.27 to 2.72)	(-3.32 to	11.92±0.89 (*13*)	(-2.92 to	(-3.68 to 1.48)	
Δ from baseline^	**-0.45**		0.32)	**+1.077**	1.07)		**0.15^**
Follow-up (*n*)	11.50±0.89 (*8*)			12.10±1.01 (*11*)			
Δ from baseline#*	**+1.0**			**+0.9**			**0.93#**
Fun Seeking (score/16)							
Baseline (*n*)	11.36±0.64 (*14*)	0.002**	>0.99	11.1±0.5 (*14*)	0.16	0.61	
After treatment (*n*)	10.00±0.59 (*11*)	(0.52 to 2.19)	(-0.78 to	12.23±0.60 (*13*)	(-2.47 to	(-2.85 to 1.34)	
Δ from baseline^	**-0.64**		0.99)	**+1.0**	0.29)		**0.01^***
Follow-up (*n*)	11.25±0.92 (*8*)			11.90±0.85 (*11*)			
Δ from baseline#*	**-0.250**			**+0.40**			**0.48#**
Reward Responsiveness (score/20)							
Baseline (*n*)	15.71±0.69 (*14*)	>0.99	0.06	16.79±0.47 (*14*)	>0.99	0.75	
After treatment (*n*)	15.45±0.80 (*11*)	(-1.77 to 2.29)	(-4.15 to	16.69±0.63 (*13*)	(-1.29 to	(-1.58 to 1.75)	
Δ from baseline^	**-0.54**		0.079)	**-0.10**	1.48)		**0.52^**
Follow-up (*n*)	17.75±0.77 (*8*)			16.70±0.89 (*11*)			
Δ from baseline#*	**+2.04**			**-0.09**			**0.20#**

			BAS (score/28)				
Baseline (*n*)	19.93±1.32 (*14*)	0.39	0.44	20.70±0.88 (*14*)	0.16	0.36	
After treatment (*n*)	18.36±1.15 (*11*)	(-1.17 to 4.30)	(-4.59 to	21.23±0.97 (*13*)	(-2.92 to	(-3.68 to 1.48)	
Δ from baseline^	**-0.72**		1.44)	**+0.23**	1.07)		**0.37^**
Follow-up (*n*)	21.50±1.40 (*8*)			20.40±1.34 (*11*)			
Δ from baseline#*	**+1.57**			**-0.30**			**0.57#**
			Hospital Anxiety and Depression Scale (HADS)				
			Anxiety (score/21)				
Baseline (*n*)	4.71±1.12 (*14*)	0.98	>0.99	7.43±1.2 (*14*)	0.86	0.14	
After treatment (*n*)	3.82±0.60 (*11*)	(-1.59 to 3.39)	(-4.69 to	7.77±1.58 (*13*)	(-4.17 to	(-1.20 to 4.52)	
Δ from baseline^	**-1.36**		3.63)	**-0.23**	3.44)		**0.51^**
Follow-up (*n*)	5.25±1.33 (*8*)			6.11±1.81 (*11*)			
Δ from baseline#*	**+0.54**			**-1.44**			**0.40#**
			Depression (score/21)				
Baseline (*n*)	4.07±1.00 (*14*)	>0.99	>0.99	6.57±0.95 (*14*)	0.28	0.08	
After treatment (*n*)	3.91±0.83 (*11*)	(-2.24 to 2.56)	(-3.50 to	5.31±1.19 (*13*)	(-1.10 to	(-1.10 to 3.74)	
Δ from baseline^	**-0.16**		3.89)	**-1.30**	3.74)		**0.74^**
Follow-up (*n*)	3.88±1.16 (*8*)			3.56±1.02 (*11*)			
Δ from baseline#*	**-0.19**			**-2.44**			**0.17#**
			Beck Depression Inventory				
			BDI-II (score/63)				
Baseline (*n*)	11.57±2.70 (*14*)	0.58	>0.99	13.00±2.20 (*14*)	>0.99	>0.99	
After treatment (*n*)	8.18±2.35 (*11*)	(-3.62 to 10.40)	(-9.79 to	12±30 (*13*)	(-10.29 to	(-12.32 to 13.88)	
Δ from baseline^	**-4.54**		9.93)	**-0.70**	22.95)		**0.55^**
Follow-up (*n*)	11.50±2.75 (*8*)			12.22±4.02 (*11*)			
Δ from baseline#*	**-0.07**			**-0.78**			**0.48#**

Behavioural changes							
Alcohol Audit							
Baseline (*n*)	2.14±0.63 (*14*)	>0.99	>0.99	2.57±0.66 (*14*)	0.26	0.31	
After treatment (*n*)	2.18±0.75 (*11*)	(-1.01 to	(-1.75 to	1.62±0.66 (*13*)	(-1.38 to 3.29)	(-2.16 to 4.11)	
Δ from baseline^	**+0.04**	0.93)	1.04)	**-0.95**			**0.32^**
Follow-up (*n*)	2.50±0.63 (*8*)			1.60±0.91 (*11*)			
Δ from baseline#*	**+0.26**			**-0.93**			**0.36#**

Data are displayed as mean±SEM (95% CI). The scores are based on set of questionnaires for VLCD and RYGB at different time points**. 1-For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group at different time point performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value***[a], before treatment vs after treatment; ***P-value***[b], before treatment vs at follow-up). **2- For between groups comparisons** (VLCD vs RYGB) of the averages of the changes from baseline; **Δ from baseline^** change from baseline at one-month on VLCD or at three months post-RYGB**; Δ from baseline#**, change from baseline at follow-up (at two-month post VLCD) or (at one-year after RYGB); ***P-value***[c] = difference in changes in treatment effect from baseline between groups (VLCD vs RYGB) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for VLCD) vs (Δ from baseline^ for RYGB) and # refer to the *P-value* of (Δ from baseline# for VLCD) vs (Δ from baseline# for RYGB); Abbreviation: VLCD, Very-Low Calorie Diet; RYGB, Roux-en-Y Gastric Bypass; Abbreviation: RYGB, Roux-en-Y Gastric Bypass; VLCD, Very Low-Calorie Diet; **BIS/BAS,** Behavioural Inhibition System/Behavioural Activation Scale; **HADS,** Hospital Anxiety and Depression Scale; **BDI-II,** Beck Depression Inventory. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

4.6.5. Health-related quality of life following VLCD

In the current study, weight loss post-VLCD did not reflect any improvement in health-related quality of life measured by SF-36 and IWQoL scales (Table 11 on Page 150).

4.6.5.1. *SF-36TM health survey (SF-36)*

No significant change was reported at any of the eight SF-36 domains post-VLCD at any time-point throughout the study period. Compared to RYGB, there was a significant improvement in physical function and bodily pain measured by SF-36 post-RYGB compared with post-VLCD (P=0.017) using unpaired t-test to the change from baseline. No significant changes between groups were observed in all other domains.

4.6.5.2. *Impact of weight on quality-of-life questionnaire (IWQoL-Lite)*

There were significant improvements in work and general health scores when measuring weight-related quality of life after one-month on the VLCD (Adjusted P=0.04 and P=0.01 respectively) compared with baseline data using a mixed-effects model with a Bonferroni post hoc test. No significant differences from baseline values between VLCD and RYGB were apparent in any domain or at any time during the study period.

Table 11: *Quality-of-life questionnaires following VLCD/RYGB*

Variables	**VLCD**	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**RYGB**	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**VLCD vs. RYGB** *P-value* [c]
			SF-36TM Health Survey (SF-36)				
			Physical Functioning (score/100)				
Baseline (*n*)	70.99±6.47 (*14*)	0.80	>0.99	48.9±7.76 (*14*)	0.056	0.0002 ***	
After treatment (*n*)	77.27±5.28 (*11*)	(-21.65 to	(-24.19 to	73.85±7.14 (*13*)	(-50.45 to	(-57.37 to -24.77)	
Δ from baseline^	**+7.191**	9.09)	12.43)	**+23.46**	0.61)		**0.22^**
Follow-up (*n*)	76.88±9.39 (*8*)			90.00±4.17 (*11*)			
Δ from baseline#*	**+0.6250**			**+40.00**			**0.0004#*** **
			Limitations due to physical health (score/100)				
Baseline (*n*)	80.36±9.51 (*14*)	>0.99	>0.99	53.57±11.68 (*14*)	0.007**	0.062	
After treatment (*n*)	81.82±8.98 (*11*)	(-36.75 to	(-47.54 to	94.23±4.15 (*13*)	(-27.20 to -	(-77.78 to 1.59)	
Δ from baseline^	**+1.545**	33.83)	52.01)	**+38.46**	9.12)		**0.06^**
Follow-up (*n*)	78.13±11.99 (*8*)			91.67±8.33 (*11*)			
Δ from baseline#*	**-3.12**			**+36.1**			**0.10#**
			Limitations due to emotional problems (score/100)				
Baseline (*n*)	77.38±10.43 (*14*)	>0.99	>0.99	61.9±10 (*14*)	0.055	0.040*	
After treatment (*n*)	81.82±8.24 (*11*)	(-20.13 to	(-48.19 to	84.62±8.10 (*13*)	(-49.11 to	(-75.90 to 7.12)	
Δ from baseline^	**+4.51**	11.25)	69.62)	**+20.51**	3.69)		**0.12^**
Follow-up (*n*)	66.67±10.91 (*8*)			96.30±3.70 (*11*)			
Δ from baseline#*	**-10.08**			+**37.04**			**0.14#**
			Energy/Fatigue (score/100)				
Baseline (*n*)	53.93±5.03 (*14*)	>0.99	>0.99	47.86±4.96 (*14*)	0.46	0.144	
After treatment (*n*)	56.82±5.36 (*11*)	(-18.23 to	(-23.79 to	53.85±6.33 (*13*)	(-28.07 to	(-34.88 to 8.37)	
Δ from baseline^	**+8.182**	12.46)	27.89)	**+6.154**	16.09)		
Follow-up (*n*)	51.88±5.59 (*8*)			61.11±7.10 (*11*)			**0.84^**
Δ from baseline#*	**-2.37**			**+12.78**			**0.17#**

Emotional well-being (score/100)							
Baseline (*n*)	75.71±5.31 (*14*)	>0.99	>0.99	70.86±5.2 (*14*)	0.29	0.072	
After treatment (*n*)	75.27±4.82 (*11*)	(-14.28 to	(-19.22 to	64.00±7.71 (*13*)	(-7.67 to	(-14.69 to -0.03)	
Δ from baseline^	**-0.54**	15.17)	30.64)	**-5.84**	21.38)		**0.28^**
Follow-up (*n*)	70.00±4.54 (*8*)			78.22±7.15 (*11*)			
Δ from baseline#*	**-5.50**			**5.33**			**0.39#**
Social Functioning (score/100)							
Baseline (*n*)	78.57±7.46 (*14*)	>0.99	0.37	62.3±7.9 (*14*)	0.63	0.028*	
After treatment (*n*)	71.59±9.84 (*11*)	(-13.79 to	(-33.78 to	69.23±7.96 (*13*)	(-34.72 to	(-50.35 to -5.56)	
Δ from baseline	**-6.13**	27.76)	9.67)	**+5.00**	20.90)		**0.64**
Follow-up (*n*)	90.63±3.92 (8)			90.28±4.55 (*11*)			
Δ from baseline#*	**+12.5**			+**20.80**			**0.46#**
Pain (score/100)							
Baseline (*n*)	73.75±6.51 (*14*)	0.43	0.10	54.8±5.8 (*14*)	0.015*	0.001**	
After treatment (*n*)	83.41±4.19 (*11*)	(-27.22 to	(-22.08 to	78.27±4.44 (*13*)	(-45.49 to -	(-48.18 to -12.74)	
Δ from baseline^	**+13.86**	7.90)	2.08)	**+22.69**	1.40)		**0.41^**
Follow-up (*n*)	83.75±6.58 (*8*)			85.28±5.58 (*11*)			
Δ from baseline#*	**+9.37**			**+30.83**			**0.01#**
General Health (score/100)							
Baseline (*n*)	56.16±5.06 (*14*)	0.77	0.73	48.39±6.34 (*14*)	0.02*	0.112	
After treatment (*n*)	61.36±5.52 (*11*)	(-17.63 to	(-24.18 to	61.25±6.01 (*13*)	(-27.94 to	(-41.23 to 5.51)	
Δ from baseline^	**+8.18**	7.23)	10.26)	**+14.42**	2.23)		**0.40^**
Follow-up (*n*)	63.13±7.00 (*8*)			66.25±8.00 (*11*)			
Δ from baseline#*	**+6.09**			**+15.14**			**0.41#**

Quality-of-Life Questionnaire (IWQoL-Lite)							
Physical Function (score/55)							
Baseline (*n*)	25.71±2.74 (*14*)	>0.99	0.38	32.57±3.5 (*14*)	0.012*	0.061	
After treatment (*n*)	24.55±2.84 (*11*)	(-2.70 to 5.04)	(-3.01 to	23.46±2.96 (*13*)	(1.87 to 16.35)	(-0.55 to 26.36)	
Δ from baseline^	**-1.90**		14.69)	**-9.69**			**0.13^**
Follow-up (*n*)	22.88±3.58 (*8*)			19.67±4.15 (*11*)			
Δ from baseline#*	**-5.62**			**-12.56**			**0.42#**
Self-Esteem (score/35)							
Baseline (*n*)	21.93±1.77 (*14*)	0.09	0.58	23.79±2.3 (*14*)	0.158	0.068	
After treatment (*n*)	17.45±2.12 (*11*)	(-1.15 to 7.80)	(-7.30 to	21.00±2.82 (*13*)	(-3.67 to 9.24)	(1.24 to 14.33)	
Δ from baseline^	**-2.72**		10.66)	**-2.54**			**0.77^**
Follow-up (*n*)	23.38±2.58 (*8*)			16.00±3.29 (*11*)			
Δ from baseline#*	**+1.75**			**-4.33**			**0.87#**
Sexual Life (score/20)							
Baseline (*n*)	9.93±1.05 (*14*)	>0.99	>0.99	13.01±1.2 (*14*)	0.232	0.037*	
After treatment (*n*)	8.91±1.56 (*11*)	(-1.89 to 3.93)	(-2.19 to	10.77±1.66 (*13*)	(-3.04 to 7.64)	(-0.87 to 10.12)	
Δ from baseline^	**-1.45**		5.29)	**-2.46**			**0.67^**
Follow-up (*n*)	9.38±1.5 (*8*)			8.44±1.22 (*11*)			
Δ from baseline#*	**-0.50**			**-5.00**			**0.17#**
Public Distress (score/25)							
Baseline (*n*)	10.36±1.07 (*14*)	0.50	>0.99	14.57±1.5 (*14*)	0.417	0.074	
After treatment (*n*)	9.27±1.2 (*11*)	(-1.02 to 3.18)	(-3.28 to	13.00±2.14 (*13*)	(-1.95 to 5.09)	(-1.07 to 10.21)	
Δ from baseline^	**-1.63**		5.49)	**-1.07**			**0.72^**
Follow-up (*n*)	10.25±1.39 (*8*)			10.00±1.95 (*11*)			
Δ from baseline#*	**-0.11**			**-4.22**			**0.29#**
Work Problems (score/20)							
Baseline (*n*)	9.64±1.24 (*14*)	0.04*	>0.99	9.85±1.07 (*14*)	0.371	0.078	
After treatment (*n*)	7.18±0.99 (*11*)	(0.09 to 4.83)	(-3.21 to	9.15±1.54 (*13*)	(-1.33 to 2.74)	(-0.41 to 5.68)	
Δ from baseline^	**-2.45**		8.74)	**-0.69**			**0.49^**
Follow-up (*n*)	8.5±0.94 (*8*)			7.22±1.26 (*11*)			
Δ from baseline#*	**-1.50**			**-2.22**			**0.32#**

			IWQoL Total (score/155)				
Baseline (*n*)	77.57±5.9 (*14*)	0.01*	>0.99	94.57±6 (*14*)	0.021*	0.008**	
After treatment (*n*)	67.36±7.05 (*11*)	(2.12 to 18.30)	(-13.44 to	77.38±10.10 (*13*)	(0.48 to	(11.09 to 55.39)	
Δ from baseline^	**-10.18**		39.33)	**-16.23**	33.89)		**0.41^**
Follow-up (*n*)	74.38±7.8 (*8*)			61.33±9.94 (*11*)			
Δ from baseline#*	**-16.75**			**-27.44**			**0.39#**

Data are displayed as mean±SEM (95% CI). The scores are based on set of questionnaires for VLCD and RYGB at different time points**. 1-For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group at different time point performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value*[a], before treatment vs after treatment; ***P-value*[b], before treatment vs at follow-up). **2- For between groups comparisons** (VLCD vs RYGB) of the averages of the changes from baseline; **Δ from baseline^** change from baseline at one-month on VLCD or at three months post-RYGB**; Δ from baseline#**, change from baseline at follow-up (at two-month post VLCD) or (at one-year after RYGB); ***P-value*[c] = difference in changes in treatment effect from baseline between groups (VLCD vs RYGB) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for VLCD) vs (Δ from baseline^ for RYGB) and # refer to the *P-value* of (Δ from baseline# for VLCD) vs (Δ from baseline# for RYGB); Abbreviation: VLCD, Very-Low Calorie Diet; RYGB, Roux-en-Y Gastric Bypass; Abbreviation: RYGB, Roux-en-Y Gastric Bypass, VLCD, Very Low-Calorie Diet. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

4.6.6. Changes in food intake based on dietary records following VLCD

A total of 17 out of 24 participants were included in this analysis. Seven were excluded for the following reasons:

- One participant developed a flare-up of rheumatoid arthritis prior to starting the diet
- Two could not adhere to the diet and did not complete 28 days of the VLCD
- One participant changed his mind prior to the start of the diet but after having completed a baseline study visit.
- Three failed to complete the food diary.

Changes in energy intake were investigated using a four-day food diary (Table 12 on Page 155). The total calorie intake decreased significantly ($P<0.0001$) by about 60% (-1173 kcal) after one-month on the VLCD and remained about 14% (-287 kcal) lower than the baseline level at 3 months (two-month after stopping the diet, $P=0.4$). The macronutrient distributions showed a significant increase in protein intake and a significant reduction in fat intake at one-month on the VLCD ($P<0.0001$). These changes returned to the baseline level two-month post-VLCD. No significant changes were observed in either carbohydrate or alcohol intake at any time during the study among the VLCD group.

***Table** 12: Changes in food, alcohol and macronutrient composition intake following VLCD*

Baseline N=17	**Three-month N=17**	**One-year N=10**	**Pre vs Three-month** *P*-value[a] (95% CI)	**Pre vs One-year** *P*-value[b] (95% CI)
Total energy intake (Kcal/day)				
1987±159	814.0±32	1700±173.2	<0.0001 (754.6 to 1592)	0.44 (-199.5 to 773.5)
Macronutrient composition				
Carbohydrates (% total kcal intake)				
43±2.00	44.19±0.8	40.61±3	>0.99 (-7.31 to 4.02)	>0.99 (-4.59 to 8.59)
Protein (% total kcal intake)				
18.12±1.00	38.49±0.9	19.41±2	<0.0001 (-5.12 to 1.39)	>0.99 (-5.30 to 1.71)
Fat (% total kcal intake)				
39±1.00	17.32±0.75	38.83±2.4	<0.0001 (-7.45 to 3.85)	>0.9999 (-6.31 to 5.86)
Alcohol intake (% total kcal intake)				
0.59±0.30	0.00±0.00	1.15±0.77	0.71 (-4.68 to 3.89)	0.99 (-4.22 to 5.02)

Data are displayed as mean±SEM (95% CI) for pre-VLCD, one-month on VLCD and two-month post-VLCD. Comparison of averages between different time points using a mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test (adjusted P-value), *P*-value[a] (pre-VLCD vs one-month on VLCD), *P*-value[b] (pre-VLCD vs two-month post-VLCD). Abbreviation: Kcal; kilocalorie

4.6.7. Anthropometric data

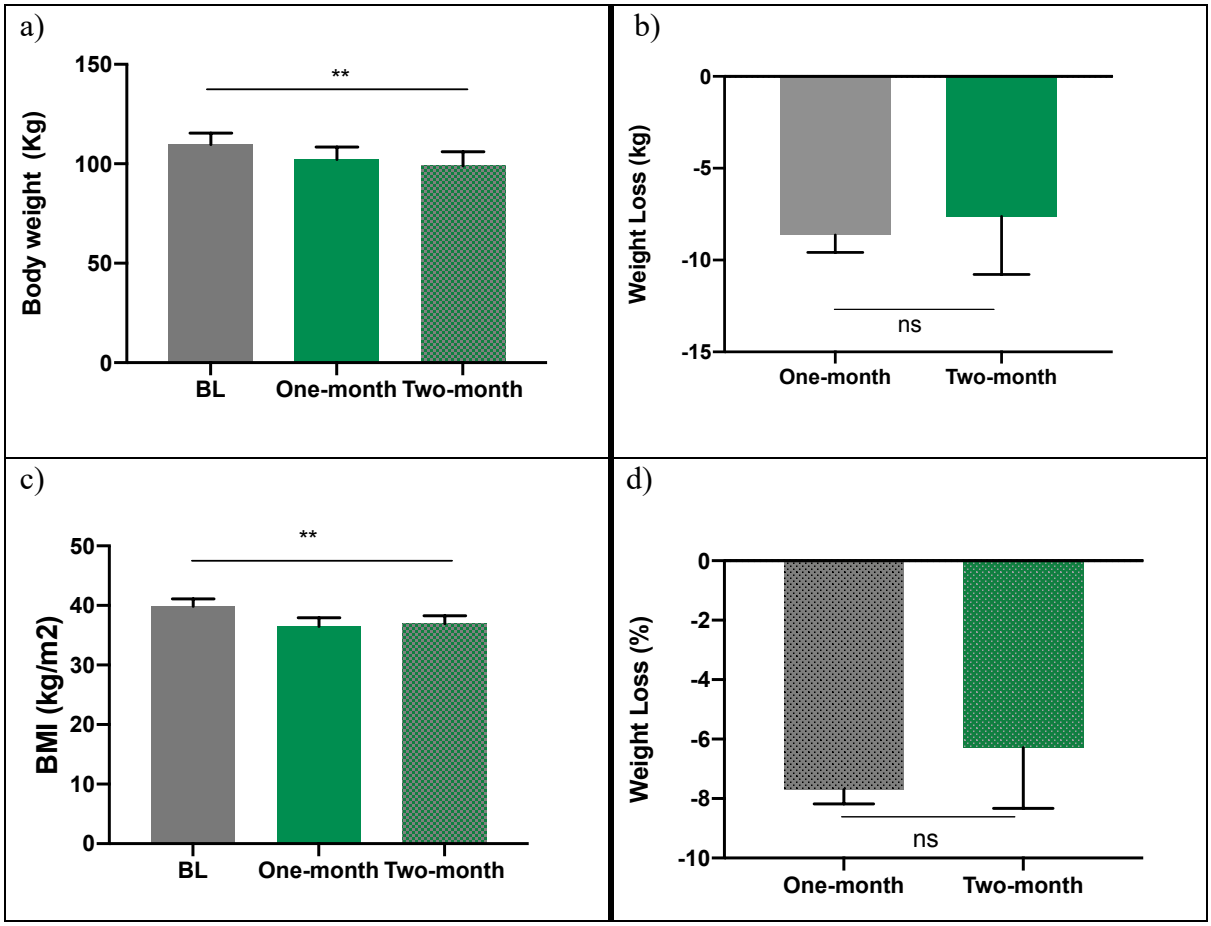
The VLCD led to significant weight loss (-9±1.9 kg) after one-month (28 days) of VLCD. Most of that weight loss was sustained for up to two-month after completing the VLCD (-8.7±4.4 kg). The mean body weight at baseline visit was 109.7±5.7 kg. After one-month on the diet this dropped to 102.2±6.24 kg, and after two-month to 98.98±7.13 kg ($p<0.0001$). This represents a significant change in body weight by -8.16±0.6%, and -7.01±2.3% at one-month on VLCD and two-month post-VLCD respectively ($P<0.0001$) for both time-points (Table 13 below; Figure 8 on page 157).

***Table** 13: Changes in body weight following VLCD*

	Baseline N=14	**Three-month N=11**	**One-year N=8**	**Pre vs Three-month** *P*-value[a] (95% CI)	**Pre vs One-year** *P*-value[b] (95% CI)
Weight (kg)	109.7±5.7	102.2±6.24	98.98±7.13	<0.0001 (4.80 to 10.32)	0.0268* (1.37 to 20.17)
BMI (kg/m^2)	39.9±1.2	36.46±1.46	36.95±1.34	<0.0001 (2.69 to 4.08)	0.0363* (0.20 to 5.60)
	One-month		**Three months**		
WL (kg)	-9±1.9		-8.7±4.4		
%WL	-8.16±0.6		-7.01±2.3		

Data are displayed as mean±SEM (95% CI) for pre-VLCD, one-month on VLCD and two-month post-VLCD. A mixed-effects model was used to compare the averages between different time points with correction for multiple comparisons using Bonferroni's post-hoc test (adjusted P-value), *P*-value[a] (Pre-VLCD vs one-month on VLCD); *P*-value[b] (Pre-VLCD vs two-month post-VLCD); WL(kg) and %WL were analysed between the two time points using a Student Paired t-test (P-value[d]).

Figure 8: *Effects of VLCD on body weight and BMI throughout the study*



Data are presented as mean±SEM at one-month and three months. A) A significant reduction in the absolute BW (kg) using a mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test. b) Weight loss in kg using a Student Paired t-test at one-month on a VLCD and two-month post-VLCD. C) Percentage weight loss post-RYGB (%) using Student Paired t-test. d) A significant reduction in BMI (kg/m^2) using mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

4.7. Discussion

4.7.1. Summary of the findings for VLCD

This study aimed to investigate the impact of VLCD diets on individuals' eating behaviour, reward food intake, psychological status, and health-related quality of life in comparison to RYGB procedures among people with obesity and T2DM. Although one-month on a VLCD led to a significant weight loss (up to 8%), which was maintained for up to two-month after the end of the VLCD, no significant modification in individuals' eating behaviour, reward drive to eat or psychological state was observed in comparison to pre-VLCD levels. Food intake data (measured using a 4-day food diary) showed a reduction in daily intake of 1137 kcal/day after following the 800kcal/day VLCD. Participants managed to maintain some of the reduction in calorie intake (-287 kcal/day) and to maintain a weight loss of up to 7% in comparison to the baseline level. However, no improvements in health-related quality of life measured by SF-36 and IWQoL scales were observed at one-month on the VLCD nor at two-month after the VLCD. As expected, the VLCD group showed a significant increase in dietary restraint as measured by EDE-Q which was maintained for up to two-month after the VLCD.

4.7.2. Eating behaviour following VLCD

Findings from this study show that VLCD does do not impact eating behaviour in the same way that RYGB surgery does. Following RYGB, many individuals show a significant reduction below baseline levels in externally induced eating (DEBQ) and cognitive restraint (TFEQ) compared with post-VLCD participants. The only change reported in post-VLCD eating behaviour in the current study was shown in the EDE-Q restraint. The difference between restraint measured by the DEBQ, which was observed to increase significantly post-RYGB, and the EDE-Q restraint that was observed to increase significantly post-VLCD, is that the former includes only successful attempts to restrict calorie intake, while the latter measures restraint regardless of whether such attempts were successful or not. Examples of questions

are: *'Do you deliberately eat foods that are slimming?'* and '*Have you tried to follow definite rules regarding your eating (for example, a calorie limit) in order to influence your shape or weight (whether or not you have succeeded)?* This increase in post-VLCD restraint is to be expected, as participants were instructed to restrict their intake to 800 kcal/day of meal replacement products that were provided to them during the study.

4.7.3. Reward drive to eat following VLCD

In contrast to the RYGB findings of the current study, there was no significant change in reward drive to eat as measured by the PFS Scale following the VLCD. Several studies (289, 294) demonstrate that people living with obesity – as compared to people of normal-weight – experience higher levels of reward drive to eat that appear to be related to higher food intake (545) and greater degrees of craving (546). Reward drive to eat may increase because of repeated exposure to and consumption of highly palatable foods. Theoretically, repeated consumption leads to increasing sensitization to the incentive importance of such foods to the point at which they significantly exceed normal ranges. The awareness of highly palatable foods as part of one's normal environment may be enhanced, thus increasing the reward drive to eat.

Until now, studies investigating the impact of reward drive to eat after short-term caloric restriction have been scarce. A reduction in reward drive to eat was found to be associated with weight loss after RYGB (294, 547). For example, Jakobsdottir et al.'s prospective fMRI study (2016) comparing BOLD activation of brain areas to food and non-food visual cues before and four weeks after a restricted diet (1000 kcal/day) in postmenopausal women with obesity found that the brain areas involved in the food reward system such as the amygdala differ substantially before and after a 4.8% weight loss (547). Although significant weight loss was achieved post-VLCD in the current study, there was no change in the reward drive to eat. this could be because

Jakobsdottir's study differs from the current study in terms of the age group, the use of fMRI instead of questionnaires, total calorie intake (1000 kcal/day vs 800 kcal/day), weight loss (4.8% vs 8%) or study design (Jakobsdottir's study used a period of isocaloric diet before and after the restricted diet). Moreover, a similar study to the current study by Theim et al. (2013) examined the reward drive to eat among people with obesity using PFS before and after fifteen weeks on a behavioural weight loss programme. The programme was administered on an individual basis using meal replacement products and focusing on individual behaviour. No details were given regarding total energy intake, but those who completed the programme (N=111) achieved an average weight loss of 9.8%. Even though the current study and the Theim study started from the same score in the PFS (2.6) and achieved similar weight loss to that achieved in the current study (9%), the impact on reward drive to eat was different, as a significant reduction in hedonic hunger was observed in the Theim cohort which was associated with weight loss (383). The current study's short timescale (only one-month) compared with Theim et al's fifteen-week study could be a potential factor for the differences in the results between the two studies. Other potentially influential factors include focusing on lifestyle and weight control behaviour, which was a missing element in the current study. Meanwhile, the number of participants in this study (N=14) is not comparable with the number in Theim's study (N=111) which is maybe also a reason for the differences in the results. In other words, the current study may be insufficiently powerful to detect the change in reward drive to eat following VLCD. This study provides preliminary data on the impact of VLCDs on the reward drive to eat measured by the PFS, but further study is warranted using larger sample sizes. The nature of the relationship between RYGB, VLCD, hedonic hunger and weight loss remains open to further exploration.

4.7.4. Psychological status, alcohol consumption and quality of life following VLCD

Unexpectedly, no change in the psychological outcomes or health-related quality of life (measured by SF-36) were reported after one-month on the VLCD, despite the >5% weight loss that was achieved. This is in contrast to previous findings, including a 10-week VLCD regime within a clinical-selected population (548) and a 16-week programme for participants with obesity and T2DM patients (549). The current findings might suggest that the current VLCD participants are in better psychological and physical condition than the surgical group. Another suggestion would be that patients who actively seek out treatment for obesity, such as RYGB candidates, might be more affected by their weight than those who are simply participating in a weight-loss study. The possibility of this study being under power is still to be considered.

There was no change in the alcohol consumption measured by AUDIT after one-month on the VLCD. To my knowledge, no studies have shown any increase in AUD within the first 3 months post-RYGB or any AUD development in VLCD. Unlike the result of health-related quality of life SF-36 scale, there were significant improvements in the work and general health domain measured by IWQoL-Lite after one-month on the VLCD (Adjusted P=0.04 and P=0.01 respectively) compared with baseline data using a mixed-effects model with a Bonferroni post hoc test. The IWQoL-Lite scale revealed predominantly weight-related quality of life, whereas the SF-36 scale assesses the generic quality of life that is also determined by other factors than weight.

4.8. Conclusion of VLCD study

In summary, the preliminary data of this study showed that there were no changes in eating behaviour, reward responses to food, psychological status, or alcohol consumption after one-month on a VLCD among participants with obesity and T2DM despite the significant weight-loss they achieved. In comparison to patients after RYGB surgery, VLCD patients rigidly restrained their intake and differ in terms of their reward drive to eat. Further study is warranted in larger samples to determine the nature of the changes between RYGB and VLCD,

4.9. Limitations

The preliminary results were seen in this study show some limitations. Firstly, the number of participants in the study is small, which implies a high risk of type-I statistical error. The study may therefore be underpowered in terms of making definitive statements about the impact of VLCD on the measured factors. The power calculation of the study was based on a 30% reduction in food intake. This was the main outcome for the study of which my study forms a part of. It suggested that ten participants per group would be adequate to give a power of 80%. Another potential limitation relates to the possibility of selection bias, which may decrease the representativeness of the study samples. Although both the VLCD and the surgical group followed the same eligibility criteria, VLCD participants were selected via advertisements while the RYGB participants were selected from the waiting list for bariatric surgery. I tried to avoid samples that do not reflect my target population by picking those who belong to certain groups. Further study is warranted to overcome the current study limitations and to determine whether or not VLCD is involved in the change in eating behaviour or reward drive to eat seeing after RYGB.

5. CHAPTER FIVE:

INFUSION STUDY (PART 1)

The Effect of a Chronic Infusion of GOP on Eating Behaviour and Food Reward in People with Obesity and Type 2 Diabetes

In the previous chapters, I established that people living with obesity and T2DM who underwent RYGB surgery experienced a reduction in reward drive to eat and a change in eating behaviour which included a reduction in dietary disinhibition and concerns about weight and shape, and that this reduction was sustained for up to one-year after the operation. None of these changes were observed to result from VLCD interventions. In this chapter, I test the hypothesis that improvements in eating behaviour and reward drive to eat following bypass surgery may be caused by changes in circulating gut hormones.

5.1. Introduction

The proposed mechanism for how RYGB brings about successful weight loss is based on profound changes in the secretion of gastrointestinal hormones that follow RYGB surgery (186, 206, 550-554), including increases in Glucagon-Like Peptide-1 (GLP-1), Oxyntomodulin (OXM) and Peptide YY (PYY) (186). These three anorexigenic hormones are secreted from the neuroendocrine L cells that are present throughout the GI tract and which respond to food intake to provoke feelings of satiety (216). Increases in satiety are not observed after equivalent weight loss using any other dietary or lifestyle interventions (187), which makes mimicking the profound changes in the secretion of gastrointestinal hormones that follow RYGB surgery a promising approach for the treatment of obesity without actually using surgery. GLP-1 acts through GLP-1 receptors (GLP1R) that are expressed in the beta cells of the pancreas, the arcuate nucleus in the brain and the hepatic vagal afferents (198). The activation of GLP1R appears to act as a satiety signal, which is transmitted through the central nervous system and the vagus nerve to the hypothalamus (198, 555) to delay gastric emptying and suppress appetite, thus reducing food intake (192). The injection of exendin (9-39), a GLP-1-receptor antagonist, has been proved to block the inhibitory effect of GLP-1 on food intake and increase body weight in rats (556, 557). Acute peripheral infusions of GLP-1 promote satiety and reduce energy intake in normal-weight men (558), participants with obesity (559), and participants

with T2DM (560). GLP-1 agonists such as Liraglutide and Semaglutide are already a recognised treatment for both diabetes (561) and obesity (133). OXM is secreted from the gut alongside GLP-1 following nutrient ingestion, and is proportional to calorie intake (211). OXM was found to work through the hypothalamus as a dual agonist of both GLP-1R and the glucagon receptors, although with less affinity than native ligands (213).

To date, no specific receptor for OXM itself in the CNS has been identified, although there is a specific binding site in the gastric mucosa. Like GLP-1, OXM has been shown to increase feelings of satiety, leading to weight loss (197, 562) by reducing food intake and increasing energy expenditure (215). Acute peripheral infusions and chronic subcutaneous injections of OXM have been found to induce weight loss by inhibiting food intake in rats (214) as well as in healthy participants (193) and participants with obesity (215). A chronic subcutaneous pre-prandial administration of OXM three times daily in a double-blinded, randomized and controlled trial resulted in a reduction in food intake and an average weight loss of 2.3 kg over a period of 4 weeks in overweight individuals and individuals with obesity (562). Intravenous infusions of OXM also reduced gastric emptying in humans (563). The suppression of food intake, stimulated energy expenditure and delayed gastric emptying are different mechanisms that could potentially play a role in the weight-lowering effects of OXM (215, 562-564). Like GLP-1 and OXM, PYY is also released in response to nutrient ingestion, and acts on the arcuate nucleus of the hypothalamus to reduce appetite, food intake and gastrointestinal motility (565-569). PYY_{3-36} (the active form which influences food intake) exerts its action through NPY receptors, mainly the Y2 receptor (Y2R) (570) found within the **CNS** and the vagus afferent (571, 572). Intravenous PYY infusion reduce food intake measured during buffet-type meals in individuals with obesity as well as normal-weight individuals (195), and also reduce ghrelin levels which may enhance anorexia (195).

Long-term PYY infusion in rodents leads to weight loss (573), while the co-administration of GLP-1 and PYY has synergistic effects in reducing calorie intake in normal-weight individuals (574). Svane et al. (2016) showed an increase in food intake of 20% after RYGB surgery when both GLP-1 and PYY were blocked (218). The direct blocking of PYY using receptor antagonists has been shown to reduce anorexic responses to gastric infusions of protein and long-chain fatty acids (575).

Postprandial GLP-1, OXM, and PYY secretion is elevated several-fold within days (190), one-month (576), six months or up to one-year (188, 191) after bypass surgery, and this effect can last for up to ten years (190). Reversing the PYY and GLP-1 responses using octreotide – which is an analogue of somatostatin that has an inhibitory effect on the release of peptide hormones – increases food-related fMRI activation in RYGB patients (414). Meanwhile, Svane et al. (2016) showed that food intake increased by 20% after RYGB surgery when both GLP-1 and PYY were blocked using Exendin 9–39 (another GLP-1 antagonist). The dual administration of GLP-1 and PYY (574, 577) or OXM and PYY (578) resulted in a synergistic or additive effect on food intake. It is thought that there is a connection between the roles of the two hormones in mediating the effects of RYGB, which means that if we inhibit one hormone, the other will compensate (218). Recent laboratory results demonstrated for the first time that a subcutaneous infusion of triple gut hormone GOP (GLP-1, OXM and PYY respectively) is highly effective in reducing food intake by an average of 32% in participants with obesity, compared with placebo (197). Moreover, the administration of GLP-1 and PYY to fasting participants mimicked the attenuation of the brain's reward activity as observed following feeding (196).

Although no study has so far investigated the effect of GOP hormones on eating behaviour, it may be implicated in changes in food preferences and eating behaviour after RYGB through increases in satiety and reduction in food intake as behaviour is influenced by hunger as well

as the perceived reward value of food (579). When the eating behaviour of patients after RYGB procedures was first investigated, Halmi et al. (1981) reported a reduction in total calorie intake and a selective reduction in the consumption of high-fat and high-carbohydrate foods (182). Many later studies reported a significant reduction in food intake alongside variations in macronutrient composition (225, 228, 425, 430, 580). Coughlin et al. (1983), for example, studied 25 patients with obesity who had undergone RYGB surgery using dietary recall. They reported a reduction of more than one third in food intake, predominantly in the fat component, one-year postoperatively (225). In the longest prospective study of its kind, Kruseman et al. (2010) demonstrated a reduction in fat intake 8 years after RYGB compared with baseline (228). Another eating behaviour seems to be necessary for successful weight-loss maintenance to change following RYGB. For instance, emotional and external eating behaviours (223, 268, 270, 458, 581) and eating disinhibition are found to alter postoperatively (221, 274) in the short and long term. Functional MRI studies have also shown that the appeal of high-calorie food pictures is reduced after RYGB surgery, and that this reduction cannot be explained just by differences in hunger levels (223).

The overall finding from the above studies is that gut hormones are elevated after RYGB surgery and have the potential to influence eating behaviour and food preferences. Exploiting this property could prove beneficial for designing future obesity treatments. This chapter explores the impact of subcutaneous infusions of anorexigenic gut hormones (GOP) on eating behaviour, food rewards and psychological health in people living with obesity and T2DM as a novel mechanism contributing to weight loss following RYGB.

5.2. Research aim

To investigate the effect of GOP and saline infusions on eating behaviour, food reward, psychological status, quality of life and post-intervention food intake in people living with obesity and T2DM in comparison to RYGB patients.

5.3. Research hypotheses

- Favourable eating behaviours are observed after exogenous gut hormone infusions that mimic those observed after RYGB surgery
- A decreased hedonic drive to consume highly palatable food is observed after exogenous gut hormone infusion, similar to after RYGB surgery
- Decreases in food intake are observed after exogenous gut hormone infusion, similar to after RYGB surgery

5.4. Methodology

This prospective single-blind observational study was aimed at exploring the effects of one-month chronic subcutaneous infusion of GOP on eating behaviour, food rewards, psychological changes and health-related quality of life in comparison to a one-month saline infusion and in comparison, to people three months after RYGB surgery. The RYGB group from chapter 3 forms the reference group against which the GOP group are compared. The study was conducted at the NIHR/Wellcome Trust Clinical Research Unit Facility at Hammersmith Hospital. The study was approved by the local ethics committee from the West London Research Ethics Committee (Reference number13/LO/1510), and written informed consent was obtained from all participants. The study was conducted according to the principles of the Declaration of Helsinki. People living with obesity and T2DM between 18 and 70 years and with BMIs of ≥ 30kg/m2 were recruited for the study. Participants were excluded if they were smokers (as this suppresses appetite) or possessed a

history of eating disorders as assessed by the SCOFF and Dutch Eating Behaviour Questionnaires.

5.4.1. Study protocol

Participants were asked to fast for at least 10 hours and to abstain from alcohol for 24 hours prior to each visit. At baseline, participants were asked to fill in a set of eating behaviour and psychological questionnaires, as well as a four-day food diary, which was repeated at one-month whilst still receiving the GOP/saline infusion, and two-month after the infusion. The intervention lasted for one-month and follow up visits were made two-month after the end of the intervention (see Chapter 2, Figure 4 on Page 85, for study visit plan).

5.4.1.1. *GOP infusion*

Participants were randomized to receive subcutaneous infusions of either a combination of three gut hormones: GLP-1_{7-36}, Oxyntomodulin and PYY_{3-36} (GOP), or of 0.9% saline (the placebo). The GOP infusion was delivered at doses of 4, 4, and 0.4 pmol/kg/min, respectively. This dose was chosen to achieve similar levels of gut hormones as those seen postprandially after RYGB (197). Participants were admitted to the research unit by the study team for four days for a baseline visit and to acclimatise them to the infusion and pump. They also received training from the study team during this time to set up the pump and the infusion. Randomisation was performed by an independent investigator using a computer table created by the Imperial Clinical Trials Unit. For the first three days of the infusion, the patients were monitored, and if any of them showed symptoms of mild nausea, the infusion was stopped for at least two hours and was not restarted until the symptoms had vanished. If the nausea was moderate to severe, or if vomiting occurred, the dose was adjusted according to the participants' tolerance and increased gradually until the study dose was reached. Participants started the infusion an hour before breakfast (between 6 am and 8 am) and stopped and

disconnected the pump half an hour after supper (between 6 pm and 8pm), giving them exposure to the infusion for roughly 12 hours every day. The pump was disconnected at night. Participants were sent home when they demonstrated their ability to set up the infusion and pump on their own. That was assessed by a team member who asked the participants to prepare the infusion and set up the pump without any help. They were given cooler bags to transport the infusion and told to store them in their freezers. Participants were interviewed and assessed weekly to check their welfare and to address concerns. Infusion sites were also checked during each visit. Before starting the infusion and throughout the study, all participants had dietetic sessions by the research dietitian at which healthy eating and lifestyle advice for weight loss was given. They were asked to follow a 600-calorie deficit diet from total daily requirements that was calculated using the Mifflin equation (255). The baseline dietary session focused on calorie counting, meal planning, portion control and the self-monitoring of dietary intake by documenting all intake of food and fluids at the time of eating. It was recommended by the dietitian in the session that participants should use the nutrition labels of the food packaging if available or the use of Carbs and Cals app which can be used on mobile phones or in book form to determine the nutrition content of the food product. In addition, the concepts of physiological and psychological hunger and gut hormones were discussed during the session. All materials to support these concepts were provided. Participants were interviewed and assessed on a weekly basis by the study team, including the dietitian, to check their welfare and to address concerns. Infusion sites were also checked during each visit. For more details see Chapter 2, Figure 4 on Page 85 for the study visit plan.

5.4.1.2. *RYGB group*

The preparation for the surgical group was like the infusion group in term of fasting and abstaining from alcohol prior to each study visit. Participants were also asked to fill in a set of eating behaviour and psychological questionnaires, as well as a four-day food diary at baseline.

However, they differed in the measured time and in the duration of the follow up. The first follow-up examination of RYGB changes in eating behaviour and dietary intake took place three months postoperatively, and the process was repeated one-year after surgery (see Chapter 2, Figure 4 on Page 85 for study visit plan). The reasons for the differences in measured time in the RYGB group in comparison to the infusion groups are as follows: (1) when the study was first designed and based on the literature available at the time, the RYGB weight loss after three months matched the one-month weight loss on the VLCD. (2) To reduce confounding effects of the initial liquid diet regime or the physical effects of surgery.

5.4.2. Outcome measures

The following primary outcome measures were obtained through questionnaires as detailed in Chapter 2:

- Changes in eating behaviour (measured using the Dutch Eating Behaviour Questionnaire (70), Three-Factor Eating Questionnaire (272) and the Eating Disorder Examination Questionnaire (278))
- Changes in the reward drive to eat (Power of Food Scale) (287)
- Changes in psychological state (The Beck Depression Inventory (295), Behavioural Inhibition and Activation System scales (301), Hospital Anxiety and Depression Scale (HADS) (309), Barratt Impulsivity Scale (323))
- Changes in psychological wellbeing and health-related quality of life. (Health-related Quality of Life Questionnaire (369, 370), Short-Form 36 Health Survey Questionnaire (346))

The secondary outcome measured was:

- Food intake as assessed by food diaries

5.4.3. Questionnaire Data

The following questionnaires were completed before the operation and were repeated three months and one-year postoperatively (See Chapter 2, **S**ections 2.4.1 on Pages 66-75 for more details).

5.4.3.1. Eating and Behaviour Questionnaires

3.4.1.1.23 *Dutch Eating Behaviour Questionnaire (DEBQ)* (70) to assess restraint, emotional, and external eating. A higher score indicates a greater tendency towards a measured response. This psychometric tool has been found to be reliable in bariatric surgery patients (259).

3.4.1.1.24 *Three-Factor Eating Questionnaire* (272) to measure cognitive restraint, disinhibition and hunger. Higher scores indicate higher levels of measured response. The questionnaire has been proved reliable in bariatric candidates (259).

3.4.1.1.25 *Eating Disorder Examination Questionnaire* (278) to assess the psychopathology of eating-disorder behaviour. Higher scores indicate higher levels of measured response. The EDEQ has been found to be adequately reliable and valid in the bariatric populations (279-281, 286).

5.4.3.2. Reward drive to eat

3.4.1.1.26 *Power of Food Scale* (287) to measure the reward drive to eat more palatable food, rather than the actual consumption of palatable foods. A higher score reflects the degree of control or power food has over an individual. This scale can be used to study eating behaviour after bariatric surgery to measure differences between homeostatic and reward drive to eat (292-294).

5.4.3.3. Psychological questionnaires

3.4.1.1.27 *The Beck Depression Inventory (BDI-II)* (295) to measure the presence and severity of depression and anxiety. Cut-off scores used were: 0–13 (minimal depression), 14–19 (mild depression), 20–28 (moderate depression) and 29–63 (severe depression). The process is considered to be a good measure of screening for clinical depression and shows with excellent internal consistency and validity in the bariatric surgery population (298-300).

3.4.1.1.28 *Behavioural Inhibition and Activation System (BIS/BAS) scales* (301) to measure sensitivity to punishment and reward. Although it has been used in several obesity and bariatric surgery studies (305-308), it has not been validated in these populations yet, so any results should be interpreted with caution.

3.4.1.1.29 *Hospital Anxiety and Depression Scale (HADS)* (309) to measure symptoms of depression and anxiety levels in general hospital patients. Cut-off scores are: 0-7 (normal); 8-10 (borderline abnormal) and 11-21 (abnormal) (310). The HADS has shown good responsiveness to change in patients operated on for morbid obesity (320).

3.4.1.1.30 *Barratt Impulsivity Scale* (323) to measure impulsiveness. A higher score represents a higher rate of impulsivity. The scale has good internal consistency and has potential clinical utility for measuring impulsiveness among selected patients (308, 332-334).

5.4.3.4. Health-related quality of life

3.4.1.1.31 *Health-related Quality of Life-Lite* (IWQOL-Lite) *Questionnaire* (369) to assess the impact of obesity on quality of life. Scores range from 0-155, with higher scores indicating a poorer quality of life. The IWQOL-Lite questionnaire is a validated and

reliable measure that gauges the impact of obesity on weight-related quality of life in normal-weight and overweight populations, including patients presenting for bariatric surgery (369, 370).

3.4.1.1.32 *Short-Form 36 Health Survey Questionnaire (SF36)* (346) to evaluate generic health-related quality of life across eight domains: physical functionality, role limitations due to physical problems, vitality, bodily pain, social functionality, role limitations due to emotional problems, mental health and general health perceptions. Scores range from 0-100, with higher scores indicating better health status. The SF-36 Survey (360) was listed as one of the instruments used in evaluating HR-QoL in bariatric patients in a systematic review and is now administered by the International Bariatric Surgery Registry (354, 356, 359, 361-363).

5.4.3.5. Behavioural change questionnaires

3.4.1.1.33 *Alcohol Use Disorders Identification Test* (AUDIT) (372) to assess alcohol use and alcohol-related consequences. AUDIT has demonstrated good reliability and convergent validity coefficients for the assessment of alcohol use in bariatric surgery populations (286, 299, 376, 377). Each question has four response choices which are added together to give an overall score. A score of 8 or over is associated with harmful or hazardous drinking, and a score of 13 or more for women and 15 or more for men points to a dependence on alcohol.

5.4.4. Food intake data

Each participant was given a food diary with detailed written instructions to record all food and drink consumed over four days, preferably two weekdays and two weekend days.

Participants were asked to provide details of cooking methods used, brand names and portion sizes.

5.4.5. Statistical data analysis

All statistical analyses were performed, and all figures were generated using GraphPad Prism 9 (GraphPad Software, San Diego, USA). Data were recorded as mean ± standard error of the mean (SEM), unless stated otherwise. All continuous data were tested for normality using the Shapiro-Wilk normality test. According to the assessments of normality, parametrical or non-parametrical tests were performed. P-values of <0.05 was considered significant. For baseline comparisons between groups, a mixed-effect model was performed for continuous data. The chi-square test was used for categorical data.

5.4.5.1. *Primary analysis (within group analysis)*

Comparisons of averages for all questionnaire data (absolute scores) including their respective subscales and food intake variables within-group (using baseline and multiple time-point data) were analysed using the mixed-effects model (overall P-value) with a Bonferroni post-hoc test adjustment (adjusted P-value) for multiple comparisons.

5.4.5.2. *Secondary analysis (between group analysis)*

Changes in score from baseline were calculated as the difference between pre-GOP and post-GOP scores versus the difference between pre-saline and post-saline or (pre-RYGB and post-RYGB scores) for each subject and analysed using an unpaired t-test.

5.5. Results:

5.5.1. Participant characteristics

5.5.1.1. *Infusion group*

A total of 34 participants s were recruited for the infusion study, of which 20 were randomised to receive GOP and 14 to receive saline. Four were excluded from the GOP and two from the saline group for the following reasons:

The GOP group:

- Two experienced technical issues with the infusion pump
- One developed a localised cutaneous reaction at the GOP infusion site after one week, which was self-limiting.
- One was unable to attend study visits.

The saline group:

- One participant on saline infusion developed gastroenteritis on the third week of infusion and was unable to complete the study.
- Another participant experienced very high glucose levels prior to the start of the study and when oral hypoglycaemic agents were stopped. The level of hyperglycaemia was deemed to be unsafe for him to continue with the study.

5.5.1.2. *RYGB group*

A total of 21 participants were recruited for the RYGB study. Seven were excluded from the questionnaire analysis for the following reasons:

- Three participants had their operations changed to sleeve gastrectomy and one other was converted to an open RYGB due to technical difficulties experienced during the operation.

- Two failed to answer the questionnaires (they were included in the food diary analysis but not in the questionnaire analysis)
- One participant experienced a deterioration of his diabetes control prior to surgery, which required the addition of multiple glucose-lowering agents for glycaemic optimisation, making him no longer eligible for the study.

Of the 79 recruited participants, data were only available for 16 participants who received GOP compared with 12 who received the saline placebo and 14 who underwent RYGB.

5.5.2. Demographics Data

The baseline characteristics for the three groups are shown in Table 14. The groups were similar in terms of anthropometric data. Unlike the RYGB group, the GOP group included more males (56%), and the saline group had similar gender distribution. There was no significant change in baseline levels in the other measured parameters (Table 14 on Page 178).

5.5.3. Questionnaire Data

The scores at baseline for each intervention are shown in Tables 15-16 on Page 182-184. The three intervention groups were similar at baseline in terms of their eating behaviour, food rewards and psychological behaviour measured using the Mixed-effects model. However, there was a significant difference between the groups at baseline in depression and anxiety levels measured by HADS. Depression scores for RYGB patients were significantly higher than for the other groups at baseline but were still within the normal range. The RYGB group also scored worse pre-surgery on weight-related quality of life measured by IWQoL and SF-36 such as sexual life, pain and physical function but scored the best in self-esteem compared to the other groups.

***Table** 14: Baseline characteristics of studied participants (GOP/Saline/RYGB)*

	GOP N=16	**Saline N=12**	**RYGB N=14**
Gender (F:M)	(7:9)	(6:6)	(12:2)
Age (years)	54.8±2.4	52.3±2.7	46.9±3.2
Weight (kg)	111.5±6.5	119.1±6.9	116.6±6.9
BMI (kg/m2)	38.5±1.6	39.5±1.5	42.4+1.6
Waist (cm)	121±4.9	123.4±4	121.9±3.2
Hip (cm)	124±4.6	126.5±2.9	133.4±4.5
Waist: Hip Ratio	0.9±0.02	0.9±0.02	0.9±0.03
Neck (cm)	43±1.5	41.6±1.2	41±1
FM (%)	38.7±1.6	42.8±1.9	46.6±1
T2DM, n (%)	13 (81.25)	8 (66.6)	11 (79)
Prediabetic, n (%)	3 (18.75)	4 (33.3)	3 (21)
Treatment, n (%)			
Diet only	9(56)	7(58)	5(36)
Metformin only	7(44)	5(42)	9(64)
On antidepressants treatment, n (%)	1 (6.25)	1 (8.3)	2(7.1)
Systolic blood pressure (mmHg)	132±10.5	128±4	133.1±4
Diastolic blood pressure (mmHg)	73.6±2.4	76.3±2.8	74±4
Heart rate (beats per min)	70.6±2.5	68.5±3.4	76±2.9
HbA1c (mmol/mol)	57.33±3.9	51.7±2.3	57.5±3.8
Fructosamine (µmol/l)	304.6±13	278.1±12.7	252.9±10

Data are presented as mean± standard error of the mean (SEM). A Mixed-effect model test was applied for comparison between groups for continuous data while categorical data (Gender, T2DM, and Prediabetic) were compared using the chi-square test. Prediabetic categories include impaired glucose tolerance, impaired fasting glucose, or HbA1c of 6.0–6.4% (42–48 mmol/mol). Abbreviations: GOP, GLP-1 OXM PYY; RYGB, Roux-en-Y Gastric Bypass; BMI, Body mass index; T2DM, Type 2 diabetes mellitus; FM, Fat mass; HbA1c, Glycated Haemoglobin.

5.5.3.1. Eating behaviour questionnaires following GOP infusion

In general, there was a significant increase in dietary restraint score measured by DEBQ at one-month using the GOP infusion that was sustained for up to two-month after the infusion in comparison to baseline level using one-way **ANOVA**, correcting for multiple comparisons using the Bonferroni post hoc test. There were no significant changes in the other eating behaviour scores as measured by a set of questionnaires after GOP infusion compared to baseline levels (one-way **ANOVA**, correcting for multiple comparisons using the Bonferroni post hoc test). There was no significant change from baseline in eating behaviour between GOP and saline infusion after one-month of infusion or at two-month post-infusion using the student unpaired t-test. However, comparing GOP to RYGB participants, three months postoperatively showed a significant reduction from baseline in external eating, disinhibition, weight and shape concerns, and food rewards compared to one-month after GOP infusion using the student unpaired t-test (Tables 17-18 on Pages 186-191).

5.5.3.1.1. The Dutch Eating Behaviour Questionnaire (DEBQ)

A significant increase in eating restraint score at one-month during GOP infusion (P=0.01) was sustained two-month after GOP infusion (P=0.006) (2.9±0.2 at baseline to 3.2±0.18 at one-month and 3.2±0.19 at two-month out of five) analysed using RM one-way **ANOVA** with the Bonferroni post-hoc test. However, the emotional and external eating scores did not differ significantly during GOP infusion nor at two-month post GOP using RM one-way **ANOVA** with Bonferroni post-hoc testing, compared to pre-infusion scores. There was no significant change from baseline between the GOP and saline group in the DEBQ-subscales (restraint, emotional or external eating) using unpaired t-tests at any time point (Table 17 on Page 185). In comparison to RYGB, there was a significant reduction from baseline (P=0.014) in external eating three months after RYGB (-0.95±0.24) compared to one-month after GOP infusion (-

0.28±0.12) using the unpaired t-test. There was no significant change from baseline in the RYGB and GOP group in eating restraint scores (P=0.10) or in emotional eating scores (P=0.86) using the unpaired t-test (Table 18 on Page 188).

5.5.3.1.2. Three-Factor Eating Questionnaire (TFEQ)

GOP infusions appeared to have no impact on TFEQ-subscales (cognitive restraint (P=0.99), disinhibition (P=0.18) and hunger (P=0.16) at any time point using RM one-way **ANOVA** with a Bonferroni post-hoc test. In comparison to the saline group, there was no significant difference in changes from baseline in all TFEQ subscales between the GOP and saline group using an unpaired t-test (Table 17 on Page 185). However, in comparison to RYGB, there was a significant reduction in change from baseline in disinhibited eating three months after RYGB (-2.39±0.63) compared to one-month after GOP infusion (0.06±0.64), measured using an unpaired t-test (P=0.01). There were no differences in the change from baseline between GOP and RYGB in the other TFEQ-subscales (cognitive restraint [P=0.05] or hunger [P=0.89]) (Table 18 on Page 188).

5.5.3.1.3. Eating Disorder Examination Questionnaire (EDE-Q)

Compared to the baseline scores, there were no significant changes in scores for restraint (P=0.07), weight (P=0.55), eating (P=0.25) or shape concerns (P=0.45) on the EDE-Q at any time after the GOP infusion using RM one-way **ANOVA** with a Bonferroni post-hoc test. Comparing changes from baseline in the GOP vs the saline group, there were no significant changes from baseline at any time point using the unpaired t-test (Table 17 on Page 185). However, in comparison to RYGB, there was a significant difference in change from baseline in weight and shape concerns (-0.92±0.39 and -0.99±0.46 respectively) at three months post-RYGB compared to one-month post GOP (0.10±0.12 and -0.34±0.30 respectively) measured using an unpaired t-test (P=0.01 for both). No changes from baseline in the other EDE-Q

subscales were observed between GOP and RYGB using the unpaired t-test (Table 18 on Page 188).

5.5.3.2. Reward drive to eat following GOP infusion

5.5.3.2.1. Power of Food Scale (PFS)

The POF baseline scores for all three groups are as follows; GOP 2.59±0.174; Saline 2.58±0.21; RYGB 3.18±0.29) (Tables 17-18 on Page 186-191). One-month after the infusion (GOP or saline) and three months after RYGB, the scores were reduced (2.33±0.19; 2.75±0.22; 2.04±0.29 respectively). GOP infusions did not appear to have any effect on preoccupation with food compared to before GOP at any time point (P=0.17, using RM one-way **ANOVA** with Bonferroni post-hoc testing). There were no significant changes from baseline scores between GOP and the saline group at any time point (Table 17 on Page 185). However, the change from baseline three months post-RYGB surgery (-1.09±0.25) showed a significant reduction in preoccupation with food, measured according to the power of food scale in comparison with the change from baseline at one-month post-GOP infusion (-0.27±0.14) using the unpaired t-test (P=0.005) (Table 18 on Page 188).

***Table** 15: Questionnaire scores at baseline across all interventions*

	GOP N=16	**Saline N=12**	**RYGB N=14**
Eating Behaviour Questionnaire			
The Dutch Eating Behaviour Questionnaire (DEBQ)			
Dietary Restraint (score/5)	2.89±0.20	2.88±0.22	2.67±0.16
Emotional eating (score/5)	2.71±0.29	2.72±0.26	2.50±0.27
External eating (score/5)	3.19±0.12	3.26±0.14	3.26±0.18
Three-Factor Eating Questionnaire (TFEQ)			
Cognitive Restraint (score/21)	9.50±1.13	9.58±1.09	10.29±1.4
Disinhibition (score/16)	7.00±0.85	6.25±0.96	8.78±0.68
Hunger (score/14)	6.56±0.59	6.79±0.61	6.36±0.75
Eating Disorder Examination Questionnaire (EDEQ)			
Restraint Eating (score/6)	1.83±0.33	1.67±0.49	1.40±0.30
Weight Concern (score/6)	2.76±0.291	2.49±0.32	3.40±0.38
Eating Concern (score/6)	0.85±0.38	0.93±0.37	1.45±0.43
Shape Concern (score/6)	3.41±0.34	3.11±0.45	3.89±0.40
Global (score/6)	2.21±0.25	2.05±0.37	2.50±0.37
Food reward Questionnaire			
Power of Food (score/5)	2.59±0.174	2.58±0.21	3.18±0.29
Psychological status Questionnaires			
Barratt Impulsiveness (score/120)	59.38±2.47	61.63±2.98	60.86±3.07
Behavioural Inhibition System/Behavioural Activation System (BIS/BAS) Scales			
Drive Seeking (score/16)	10.56±0.66	11.58±0.79	11.00±6.70
Fun Seeking (score/16)	11.25±0.32	11.58±0.70	11.10±0.50
Reward Responsiveness (score/20)	16.88±0.43	17.08±0.65	16.79±0.47
BAS (score/28)	20.56±0.88	18.04±1.27	20.70±0.88
Hospital Anxiety and Depression Scale (HADS)			
Anxiety (score/21)	6.25±0.89	4.08±0.84	7.40±1.20
Depression (score/21)	3.13±0.78	4.38±0.74	6.57±0.95*

Beck Depression Inventory (BDI-II)	11.50±2.85	10.04±2.27	13.00±2.20
Behavioural changes			
Alcohol Audit (score/40)	5.00±1.13	5.25±1.11	2.57±0.66

Data are presented as mean±SEM. Mixed-effect model test applied for comparison between groups at baseline. Abbreviations: GOP GLP-1 OXM PYY; RYGB, Roux-en-Y Gastric Bypass. Abbreviation: RYGB, Roux-en-Y Gastric Bypass; VLCD, Very Low-Calorie Diet; BIS/BAS, Behavioural Inhibition System/Behavioural Activation Scale; HADS, Hospital Anxiety and Depression Scale; BDI-II, Beck Depression Inventory. *P<0.05; **P<0.01; ***P<0.001

***Table** 16: Continued questionnaire scores at baseline across all interventions*

	GOP N=16	**Saline N=12**	**RYGB N=14**
SF-36TM Health Survey (SF-36) (*Higher scores indicate better health status)*			
Physical Functioning (score/100)	80.31±4.32	65.83±9.00	48.9±7.76**
Limitations due to physical health (score/100)	76.56±8.68	76.04±10.03	53.57±11.68
Limitations due to emotional problems (score/100)	81.25±9.11	73.61±12.22	61.9±10
Energy/Fatigue (score/100)	54.06±6.18	55.83±6.16	47.86±4.96
Emotional well-being (score/100)	78.00±4.31	79.33±4.79	70.86±5.20
Social Functionality (score/100)	78.91±6.53	79.17±7.74	62.3±7.9
Pain (score/100)	75.63±5.56	72.81±6.45	54.8±5.8 *
General Health (score/100)	60.32±4.30	54.17±5.35	48.39±6.34
Quality-of-Life Questionnaire (IWQoL-Lite) *(Lower scores indicate better health status)*			
Physical Function (score/55)	24.50±2.17	23.58±2.51	23.79±2.30
Self-Esteem (score/35)	21.38±2.05	18.21±1.74	13.01±1.20**
Sexual Life (score/20)	7.75±0.75	8.38±1.23	14.57±1.5 **
Public Distress (score/25)	10.75±1.39	10.00±1.67	9.85±1.07
Work Problems (score/20)	7.63±0.65	7.08±1.01	7.22±1.3
IWQoL Total (score/155)	72.00±5.89	67.25±6.66	94.57±6 **

Data are presented as mean±SEM. Mixed-effect model test applied for comparison between groups; Abbreviations: GOP GLP-1 OXM PYY; RYGB, Roux-en-Y Gastric Bypass. *P<0.05; **P<0.01; ***P<0.001

Table 17: *Eating behaviour and food reward following GOP/Saline*

Variables	**GOP** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**Saline** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**GOP vs. Saline** *P-value*[c]
Eating Behaviour Questionnaire							
The Dutch Eating Behaviour Questionnaire (DEBQ)							
Dietary Restraint (score/5)							
Baseline (*n*)	2.9±0.2 *(16)*	0.01*	0.006**	2.88±0.21 *(12)*	0.98	>0.99	
After treatment (*n*)	3.2±0.18 *(16)*	(-26.49 to	(-18.35 to 3.15)	2.99±0.13 *(12)*	(-0.58 to 0.35)	(-0.55 to 0.40)	
Δ from baseline^	**+0.30±0.14**	14.09)		**+0.12±0.16**			**0.36**^
Follow-up (*n*)	3.2±0.19 *(16)*			2.95±0.1 *(12)*			
Δ from baseline[#]	**+0.36±0.96**			**+0.08±0.17**			**0.13**[#]
Emotional Eating (score/5)							
Baseline (*n*)	2.712±0.28 *(16)*	0.18	0.16	2.72±0.26 *(12)*	0.13	0.05	
After treatment (*n*)	2.389±0.28 *(16)*	(-0.11 to	(-0.11 to 0.87)	2.5±0.25 *(12)*	(-0.06 to 0.49)	(-0.01 to0.49)	
Δ from baseline^	**-0.32±0.16**	0.75)		**-0.22±0.09**			**0.62**^
Follow-up (*n*)	2.33±0.26 *(16)*			2.33±0.27 *(12)*			
Δ from baseline[#]	**-0.38±0.18**			**-0.39±0.14**			**0.97**[#]
External Eating (score/5)							
Baseline (*n*)	3.19±0.12 *(16)*	0.11	0.35	3.26±0.14 *(12)*	>0.99	0.09	
After treatment (*n*)	2.92±0.13 *(16)*	(-0.05 to	(-0.15 to 064)	3.19±0.12 *(12)*	(-0.33 to 0.46)	(-0.04 to 0.56)	
Δ from baseline^	**-0.28±0.12**	0.59)		**-0.07±0.14**			**0.97**^
Follow-up (*n*)	2.95±0.14 *(16)*			3.0±0.11 *(12)*			
Δ from baseline[#]	**-0.24±0.15**			**-0.26±0.11**			**0.94**[#]
Three-Factor Eating Questionnaire (TFEQ)							
Cognitive Restraint (score/21)							
Baseline (*n*)	9.50±1.13 *(16)*	>0.99	>0.99	9.58±1.09 *(12)*	>0.99	>0.99	
After treatment (*n*)	9.50±1.07 *(16)*	(-2.71 to	(-2.24 to 2.12)	8.91±1.09 *(12)*	(-1.51 to 2.84)	(-1.69 to 3.03)	
Δ from baseline^	**0.00±1.00**	2.71)		**-0.67±0.77**			**0.62**^
Follow-up (*n*)	9.56±1.18 *(16)*			8.92±1.07 *(12)*			
Δ from baseline[#]	**+0.06±0.80**			**-0.67±0.83**			**0.54**[#]

			Disinhibition (score/16)				
Baseline (*n*)	7.00±0.85 (16)	>0.99	0.40	6.25±0.96 *(12)*	0.25	>0.99	
After treatment (*n*)	7.06±0.83 *(16)*	(-1.77 to	(-2.70 to 0.70)	7.50±0.69 *(12)*	(-3.12 to 0.62)	(-1.73 to 0.89)	
Δ from baseline^	**+0.06±0.64**	1.65)		**+1.25±0.66**			**0.21^**
Follow-up (*n*)	8.00±0.83 *(16)*			6.67±0.72 *(12)*			
Δ from baseline#	**-1.00±0.63**			**+0.42±0.46**			**0.49#**
			Hunger (score/14)				
Baseline (*n*)	6.56±0.59 *(16)*	>0.99	0.20	6.79±0.61 *(12)*	>0.99	>0.99	
After treatment (*n*)	7.13±0.49 *(16)*	(-2.17 to	(-2.53 to 0.40)	6.67±0.49 *(12)*	(-1.19 to 1.45)	(-1.14 to 1.23)	
Δ from baseline^	**+0.56±0.59**	1.05)		**-0.13±0.47**			**0.39^**
Follow-up (*n*)	7.63±0.61 *(16)*			6.75±0.69 *(12)*			
Δ from baseline#	**+1.06±0.54**			**-0.04±0.42**			**0.14#**
			Eating Disorder Examination Questionnaire (EDEQ)				
			Restraint Eating (score/6)				
Baseline (*n*)	1.83±0.33 *(16)*	0.05	0.82	1.67±0.49 *(12)*	0.09	>0.99	
After treatment (*n*)	2.85±0.36 *(16)*	(-2.06 to	(-1.48 to 0.61)	3.18±0.41 *(12)*	(-3.27 to 0.23)	(-1.40 to 1.14)	
Δ from baseline^	**+1.03±0.38**	0.01)		**+1.51±0.62**			**0.48^**
Follow-up (*n*)	2.26±0.41 *(16)*			1.80±0.36 *(12)*			
Δ from baseline#	**+0.44±0.39**			**+0.13±0.45**			**0.61#**
			Weight Concern (score/6)				
Baseline (*n*)	2.76±0.29 *(16)*	>0.99	>0.99	2.49±0.32 *(12)*	0.50	>0.99	
After treatment (*n*)	2.86±0.25 *(16)*	(-0.42 to	(-0.73 to 0.35)	2.85±0.25 *(12)*	(-1.04 to 0.33)	(-0.85 to 0.90)	
Δ from baseline^	**+0.10±0.12**	0.22)		**+0.36±0.24**			**0.31^**
Follow-up (*n*)	2.95±0.33 *(16)*			2.47±0.34 *(12)*			
Δ from baseline#	**+0.19±0.19**			**-0.03±0.31**			**0.55#**
			Eating Concern (score/6)				
Baseline (*n*)	0.85±0.38 *(16)*	>0.99	0.46	0.93±0.37 *(12)*	>0.99	>0.99	
After treatment (*n*)	0.90±0.29 *(16)*	(-0.63 to	(-1.15 to 0.33)	0.78±0.29 *(12)*	(-0.71 to 1.01)	(-0.57 to 0.69)	
Δ from baseline^	**+0.05±0.21**	0.53)		**-0.15±0.30**			**0.59^**
Follow-up (*n*)	1.26±0.39 *(16)*			0.87±0.26 *(12)*			
Δ from baseline#	**+0.41±0.27**			**-0.06±0.22**			**0.10#**

			Shape Concern (score/6)				
Baseline (*n*)	3.41±0.34 *(16)*	0.81	>0.99	3.11±0.45 *(12)*	0.34	0.49	
After treatment (*n*)	3.06±0.35 *(16)*	(-0.47 to	(-0.73 to 0.35)	2.70±0.43 *(12)*	(-0.26 to 1.08)	(-0.27 to 0.86)	
Δ from baseline^	**-0.34±0.30**	1.15)		**-0.41±0.24**			**0.05^**
Follow-up (*n*)	3.34±0.39 *(16)*			2.81±0.48 *(12)*			
Δ from baseline#	**-0.06±0.29**			**-0.29±0.19**			**0.10#**
			Global (score/6)				
Baseline (*n*)	2.21±0.25 *(16)*	0.35	0.80	2.05±0.37 *(12)*	0.48	>0.99	
After treatment (*n*)	2.42±0.21 *(16)*	(-0.56 to	(-0.73 to 0.29)	2.38±0.22 *(12)*	(-0.96 to 0.29)	(-0.47 to 0.57)	
Δ from baseline^	**+0.21±0.13**	0.134)		**+0.33±0.22**			**0.10^**
Follow-up (*n*)	2.43±0.33 *(16)*			1.99±0.28 *(12)*			
Δ from baseline#	**+0.22±0.19**			**-0.05±0.18**			**0.40#**
			Food Reward Questionnaire				
			Power of Food(score/5)				
Baseline (*n*)	2.59±0.17 *(16)*	0.24	0.62	2.58±0.21 *(12)*	>0.99	0.21	
After treatment (*n*)	2.33±0.19 *(16)*	(-0.12 to	(-0.24 to 0.71)	2.75±0.22 *(12)*	(-0.83 to 0.48)	(-0.14 to 0.79)	
Δ from baseline^	**-0.27±0.14**	0.66)		**+0.18±0.23**			**0.94^**
Follow-up (*n*)	2.36±0.19 *(16)*			2.25±0.19 *(12)*			
Δ from baseline#	**-0.23±0.18**			**-0.33±0.16**			**0.70#**

Data are displayed as mean±SEM (95% CI). The scores are based on set of questionnaires at baseline, one-month on infusion (after treatment), and two-month post the infusion (follow-up). **1- For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value*** [a], before treatment vs after treatment; ***P-value*** [b], before treatment vs at follow-up). **2- For between groups comparisons** (GOP vs Saline) of the averages of the changes from baseline; **Δ from baseline^**, change from baseline at one-month on the infusion**; Δ from baseline#**, change from baseline at follow-up (two-month post the infusion); ***P-value*** [c] = difference in changes in treatment effect from baseline between groups (GOP vs Saline) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for GOP) vs (Δ from baseline^ for Saline) at one-month of infusion and # refer to the *P-value* of (Δ from baseline# for GOP) vs (Δ from baseline# for Saline) at two-month post-infusion. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. Abbreviation: GOP, GLP-1 OXM 3-36PYY

Table 18: *Eating behaviour and food reward following GOP/RYGB*

Variables	**GOP** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**RYGB** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**GOP vs. RYGB** *P-value*[c]
<u>Eating Behaviour Questionnaire</u>							
The Dutch Eating Behaviour Questionnaire (DEBQ)							
Dietary Restraint (score/5)							
Baseline (*n*)	2.9±0.2 *(16)*	0.01*	0.006**	2.67±0.16 (*14*)	0.007 **	0.20	
After treatment (*n*)	3.2±0.18 *(16)*	(-26.49 to	(-18.35 to	3.48±0.26 (*13*)	(-1.45 to -0.16)	(-1.52 to 0.59)	
Δ from baseline^	**+0.30±0.14**	14.09)	3.15)	**+0.75±0.23**			**0.10^**
Follow-up (*n*)	3.2±0.19 *(16)*			3.14±0.43 (*11*)			
Δ from baseline#	**+0.36±0.96**			**+0.53±0.39**			
Emotional Eating (score/5)							
Baseline (*n*)	2.712±0.28 *(16)*	0.18	0.16	2.5±0.27 (*14*)	0.109	0.56	
After treatment (*n*)	2.389±0.28 *(16)*	(-0.11 to 0.75)	(-0.11 to 0.87)	2.15±0.25 (*13*)	(-0.27 to 1.24)	(-1.10 to 1.14)	
Δ from baseline^	**-0.32±0.16**			**-0.37±0.21**			**0.86^**
Follow-up (*n*)	2.33±0.26 *(16)*			2.51±0.46 (*11*)			
Δ from baseline#	**-0.38±0.18**			**-0.18±0.31**			
External Eating (score/5)							
Baseline (*n*)	3.19±0.12 *(16)*	0.11	0.35	3.26±0.18 (*14*)	0.002 **	0.07	
After treatment (*n*)	2.92±0.13 *(16)*	(-0.05 to 0.59)	(-0.15 to 064)	2.29±0.24 (*13*)	(0.31 to 1.65)	(-0.14 to 1.85)	
Δ from baseline^	**-0.28±0.12**			**-0.95±0.24**			**0.01^***
Follow-up (*n*)	2.95±0.14 *(16)*			2.41±0.34 (*11*)			
Δ from baseline#	**-0.24±0.15**			**-0.72±0.36**			
Three-Factor Eating Questionnaire (TFEQ)							
Cognitive Restraint (score/21)							
Baseline (*n*)	9.50±1.13 *(16)*	>0.99	>0.99	10.29±1.4 (*14*)	0.11	0.12	
After treatment (*n*)	9.50±1.07 *(16)*	(-2.71 to 2.71)	(-2.24 to 2.12)	6.08±1.29 (*13*)	(-0.79 to 9.21)	(-1.23 to	
Δ from baseline^	**+0.00±1.00**			**-3.9±1.83**		11.58)	**0.05^**
Follow-up (*n*)	9.56±1.18 *(16)*			5.11±1.62 (*11*)			
Δ from baseline#	**+0.06±0.80**			**-4.89±2.34**			

			Disinhibition (score/16)				
Baseline (*n*)	7.00±0.85 *(16)*	>0.99	0.40	8.78±0.68 (*14*)	0.002**	0.013*	
After treatment (*n*)	7.06±0.83 *(16)*	(-1.77 to 1.65)	(-2.70 to 0.70)	6.23±0.57 (*13*)	(0.84 to 4.27)	(0.70 to 5.98)	
Δ from baseline^	**+0.06±0.64**			**-2.39±0.63**			
Follow-up (*n*)	8.00±0.83 *(16)*			5.44±0.96 (*11*)			**0.01*^**
Δ from baseline#	**+1.00±0.63**			**-3.00±0.62**			
			Hunger (score/14)				
Baseline (*n*)	6.56±0.59 *(16)*	>0.99	0.20	6.36±0.75 (*14*)	0.42	0.21	
After treatment (*n*)	7.13±0.49 *(16)*	(-2.17 to 1.05)	(-2.53 to 0.40)	7.31±0.61 (*13*)	(-3.26 to 1.36)	(-2.77 to 1.93)	
Δ from baseline^	**+0.56±0.59**			**+0.69±0.84**			
Follow-up (*n*)	7.63±0.61 *(16)*			6.78±0.57 (*11*)			**0.89^**
Δ from baseline#	**+1.06±0.54**			**+1.11±0.82**			
			Eating Disorder Examination Questionnaire (EDEQ)				
			Restraint Eating (score/6)				
Baseline (*n*)	1.83±0.33 *(16)*	0.05	0.82	1.44±0.33 (*14*)	0.26	0.367	
After treatment (*n*)	2.85±0.36 *(16)*	(-2.06 to 0.01)	(-1.48 to 0.61)	2.32±0.52 (*13*)	(-2.69 to 0.92)	(-2.32 to 1.25)	
Δ from baseline^	**+1.03±0.38**			**+0.76±0.66**			
Follow-up (*n*)	2.26±0.41 *(16)*			1.98±0.60 (*11*)			**0.72^**
Δ from baseline#	**+0.44±0.39**			**+0.62±0.65**			
			Weight Concern (score/6)				
Baseline (*n*)		>0.99	>0.99		0.035*	0.048*	
After treatment (*n*)	2.76±0.29 *(16)*	(-0.42 to 0.22)	(-0.73 to 0.35)	3.4±0.38 (*14*)	(0.09 to 1.97)	(0.19 to 3.16)	
Δ from baseline^	2.86±0.25 *(16)*			2.52±0.35 (*13*)			
Follow-up (*n*)	**+0.10±0.12**			**-0.92±0.39**			**0.01*^**
Δ from baseline#	2.95±0.33 *(16)*			1.76±0.42 (*11*)			
	+0.19±0.19			**-1.20±0.52**			
			Eating Concern (score/6)				
Baseline (*n*)	0.85±0.38 *(16)*	>0.99	0.46	1.45±0.44 (*14*)	0.314	0.312	
After treatment (*n*)	0.90±0.29 *(16)*	(-0.63 to 0.53)	(-1.15 to 0.33)	0.85±0.28 (*13*)	(-0.99 to 2.18)	(-0.87 to 2.53)	
Δ from baseline^	**+0.05±0.21**			**-0.70±0.57**			**0.19^**
Follow-up (*n*)	1.26±0.39 *(16)*			0.62±0.43 (*11*)			
Δ from baseline#	**+0.41±0.27**			**-0.61±0.62**			

			Shape Concern (score/6)				
Baseline (*n*)	3.41±0.34 *(16)*	0.81	>0.99	3.89±0.40 (*14*)	0.22	0.096	
After treatment (*n*)	3.06±0.35 *(16)*	(-0.47 to 1.15)	(-0.73 to 0.35)	3.01±0.47 (*13*)	(-0.37 to 2.14)	(0.06 to 1.98)	
Δ from baseline^	**-0.34±0.30**			**-0.99±0.46**			
Follow-up (*n*)	3.34±0.39 *(16)*			2.05±0.53 (*11*)			**0.01^***
Δ from baseline#	**-0.06±0.29**			**-1.22±0.65**			
			Global (score/6)				
Baseline (*n*)	2.21±0.25 *(16)*	0.35	0.80	2.5±0.37 (*14*)	0.290	0.186	
After treatment (*n*)	2.42±0.21 *(16)*	(-0.56 to	(-0.73 to 0.29)	2.18±0.33 (*13*)	(-0.72 to 1.40)	(-0.27 to 2.13)	
Δ from baseline^	**+0.21±0.13**	0.134)		**-0.43±0.38**			
Follow-up (*n*)	2.43±0.33 *(16)*			1.59±0.40 (*11*)			**0.16^**
Δ from baseline#	**+0.22±0.19**			**-0.61±0.42**			
			Food Reward Questionnaire				
			Power of Food(score/5)				
Baseline (*n*)	2.59±0.17 *(16)*	0.24	0.62	3.18±0.29 (*14*)	0.0009***	0.005 **	
After treatment (*n*)	2.33±0.19 *(16)*	(-0.12 to 0.66)	(-0.24 to 0.71)	2.04±0.29 (*13*)	(0.47 to 1.81)	(0.31 to 2.31)	
Δ from baseline^	**-0.27±0.14**			**-1.09±0.25**			
Follow-up (*n*)	2.36±0.19 *(16)*			1.87±0.26 (*11*)			**0.005**^**
Δ from baseline#	**-0.23±0.18**			**-1.35±0.37**			

Data are displayed as mean±SEM (95% CI). The scores are based on set of questionnaires for GOP and RYGB at different time points**. 1-For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group at different time point performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value***[a], before treatment vs after treatment; ***P-value***[b], before treatment vs at follow-up). **2- For between groups comparisons** (GOP vs RYGB) of the averages of the changes from baseline; **Δ from baseline^** change from baseline at one-month on GOP or at three months post-RYGB**; Δ from baseline#**, change from baseline at follow-up (at two-month post GOP) or (at one-year after RYGB); ***P-value***[c] = difference in changes in treatment effect from baseline between groups (GOP vs RYGB) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for GOP) vs (Δ from baseline^ for RYGB) and # refer to the *P-value* of (Δ from baseline# for GOP) vs (Δ from baseline# for RYGB); *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001; Abbreviation: GOP, GLP-1 OXM 3-36PYY; RYGB, Roux-en-Y Gastric Bypass

5.5.3.3. Psychological and behavioural changes following GOP

Other psychological measures and alcohol consumption showed no significant changes in all variables at any time point after GOP compared with baseline level using one-way **ANOVA**. There were no changes from baseline between GOP vs saline nor between GOP vs RYGB using unpaired t-tests at any time point. The saline group showed a significant reduction from baseline in impulsivity (-5.04±1.79) in comparison to GOP (0.75±1.50) two-month after the infusion using an unpaired t-test P=0.004 (Table 19 on Page 192). No significant changes from baseline in GOP compared to saline or RYGB groups were observed in any other scales (Table 20 on Page 195).

Table 19: *Psychological and behavioural status following GOP/Saline*

Variables	**GOP** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**Saline** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**GOP vs. Saline** *P-value* [c]
<u>Psychological status Questionnaires</u>							
Barratt Impulsiveness (score/120)							
Baseline (*n*)	59.38±2.47 *(16)*	>0.99 (-2.13 to 3.76)	>0.999 (-3.32 to 4.82)	61.63±2.98 *(12)*	0.37 (-0.34 to 2.50)	0.03* (1.78 to 2.58)	**0.18**^
After treatment (*n*)	58.56±2.62 *(16)*			59.92±3.46 *(12)*			
Δ from baseline^	**+0.81±1.09**			**-1.71±1.22**			
Follow-up (*n*)	58.63±2.92 *(16)*			56.58±3.51 *(12)*			
Δ from baseline#*	**+0.75±1.50**			**-5.04±1.79**			**0.004**** #
Behavioural Inhibition System/Behavioural Activation System (BIS/BAS) Scales							
Drive Seeking (score/16)							
Baseline (*n*)	10.56±0.66 *(16)*	0.99 (-0.95 to 2.08)	>0.99 (-1.61 to 1.11)	11.58±0.79 *(12)*	0.41 (-0.63 to 2.29)	>0.999 (-1.36 to 2.53)	**0.73**^
After treatment (*n*)	10.00±0.41 *(16)*			10.75±0.74 *(12)*			
Δ from baseline^	**+0.56±0.56**			**+0.83±0.52**			
Follow-up (*n*)	10.81±0.55 *(16)*			11.00±0.66 *(12)*			
Δ from baseline#*	**-0.25±0.50**			**-0.58±-0.69**			**0.32**#
Fun Seeking (score/16)							
Baseline (*n*)	11.25±0.32 *(16)*	0.07 (-0.43 to 2.57)	>0.99 (-1.03 to 1.65)	11.58±0.70 *(12)*	0.52 (-0.87 to 2.70)	0.24 (-0.97 to 5.14)	**0.68**^
After treatment (*n*)	9.75±0.43 *(16)*			10.67±0.69 *(12)*			
Δ from baseline^	**-1.50±0.39**			**-0.92±0.63**			
Follow-up (*n*)	10.94±0.37 *(16)*			10.33±0.79 *(12)*			
Δ from baseline#*	**-0.31±0.49**			**-1.25±0.82**			**0.11**#
Reward Responsiveness (score/20)							
Baseline (*n*)	16.88±0.43 *(16)*	0.006** (0.33 to 2.05)	>0.99 (-0.78 to 1.53)	17.08±0.65 *(12)*	>0.99 (-1.04 to 1.21)	0.72 (-0.53 to 1.37)	**0.52**^
After treatment (*n*)	15.69±0.34 *(16)*			17.00±0.63 *(12)*			
Δ from baseline^	**-1.19±0.31**			**-0.08±0.39**			
Follow-up (*n*)	16.50±0.48 *(16)*			16.67±0.57 *(12)*			
Δ from baseline#*	**-0.38±0.42**			**-0.42±0.34**			**0.31**#

				BAS (score/28)			
Baseline (*n*)	20.56±0.88 *(16)*	>0.99	0.96	18.04±1.27 *(12)*	>0.99	0.78	
After treatment (*n*)	20.31±1.04 *(16)*	(-1.15 to		18.00±1.45 *(12)*		(-1.67 to	
Δ from baseline^	**-0.25±0.52**	1.65)	(-1.02 to	**-0.04±0.88**	(-2.43 to	4.09)	**0.60^**
Follow-up (*n*)	19.94±1.11 *(16)*		2.27)	16.83±1.65 *(12)*	2.51)		
Δ from baseline#*	**-0.63±0.61**			**-1.21±0.50**			**0.39#**
			Hospital Anxiety and Depression Scale (HADS)				
			Anxiety (score/21)				
Baseline (*n*)	6.25±0.89 *(16)*	0.83	>0.99	4.08±0.84 *(12)*	>0.99	>0.99	
After treatment (*n*)	5.56±0.88 *(16)*			3.92±0.71 *(12)*		(-1.27 to	
Δ from baseline^	**-0.69±0.61**	(-0.96 to	(-1.39 to	**-0.17±0.66**	(-1.69 to	1.94)	**0.57^**
Follow-up (*n*)	6.25±0.97 *(16)*	2.33)	1.39)	3.75±0.65 *(12)*	2.03)		
Δ from baseline#*	**0.00±0.52**			**-0.33±0.57**			**0.67#**
				Depression (score/21)			
Baseline (*n*)	3.13±0.78 *(16)*	>0.99	0.73	4.38±0.74 *(12)*	>0.99	>0.99	
After treatment (*n*)	3.56±0.92 *(16)*			4.08±0.77 *(12)*		(-0.73 to	
Δ from baseline^	**+0.44±0.49**	(-1.78 to	(-2.01 to	**-0.29±0.32**	(-0.60 to	1.15)	**0.26^**
Follow-up (*n*)	3.75±0.85 *(16)*	0.91)	0.76)	4.17±0.67 *(12)*	1.18)		
Δ from baseline#*	**+0.63±0.51**			**-0.21±0.33**			**0.22#**
			Beck Depression Inventory				
			BDI-II (score/63)				
Baseline (*n*)	11.50±2.85 *(16)*	0.25	0.21	10.04±2.27 *(12)*	0.45	0.52	
After treatment (*n*)	9.56±2.29 *(16)*			8.08±1.45 *(12)*			
Δ from baseline^	**-1.9±1.05**	(-0.88 to	(-1.09 to	**-1.96±1.27**	(-1.63 to	(-2.16 to	**0.98^**
Follow-up (*n*)	8.75±2.68 *(16)*	4.76)	6.59)	7.75±1.16 *(12)*	5.54)	6.74)	
Δ from baseline#*	**-2.75±1.43**			**-2.29±1.58**			**0.83#**

Behavioural changes

Alcohol Audit

Baseline (*n*)	5.00±1.13 *(16)*	0.43	>0.99	5.25±1.10 *(12)*	0.95	>0.99	
After treatment (*n*)	4.13±0.99 *(16)*			5.83±1.48 *(12)*			
Δ from baseline^	**-0.88±0.57**	(-0.66 to	(-1.19 to	**-0.58±0.56**	(-2.15 to	(-1.74 to	**0.18^**
Follow-up (*n*)	4.31±1.32 *(16)*	2.41)	2.57)	5.17±1.35 *(12)*	0.99)	0.90)	
Δ from baseline#*	**-0.69±0.69**			**-0.08±0.65**			**0.08#**

Data are displayed as mean±SEM (95% CI). The scores are based on set of questionnaires at baseline, one-month on infusion (after treatment), and two-month post the infusion (follow-up). **1- For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value*** [a], before treatment vs after treatment; ***P-value*** [b], before treatment vs at follow-up). **2- For between groups comparisons** (GOP vs Saline) of the averages of the changes from baseline; **Δ from baseline^**, change from baseline at one-month on the infusion**; Δ from baseline#**, change from baseline at follow-up (two-month post the infusion); ***P-value*** [c] = difference in changes in treatment effect from baseline between groups (GOP vs Saline) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for GOP) vs (Δ from baseline^ for Saline) at one-month of infusion and # refer to the *P-value* of (Δ from baseline# for GOP) vs (Δ from baseline# for Saline) at two-month post-infusion. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. Abbreviation: GOP, GLP-1 OXM 3-36PYY; **BIS/BAS,** Behavioural Inhibition System/Behavioural Activation Scale; **HADS,** Hospital Anxiety and Depression Scale; **BDI-II,** Beck Depression Inventory.

Table 20: *Psychological and behaviour status following GOP/RYGB*

Variables	**GOP** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**RYGB** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**GOP vs. RYGB** *P-value*[c]
Psychological status Questionnaires							
Barratt Impulsiveness (score/120)							
Baseline (*n*)	59.38±2.47 *(16)*	>0.99	>0.99	60.86±3.07 (*14*)	>0.999	>0.99	
After treatment (*n*)	58.56±2.62 *(16)*	(-2.13 to	(-3.32 to	62.54±2.59 (*13*)	(-9.43 to	(-10.88 to	
Δ from baseline^	**+0.81±1.09**	3.76)	4.82)	**+1.69±2.84**	6.07)	8.39)	**0.44^**
Follow-up (*n*)	58.63±2.92 *(16)*			62.10±4.13 (*11*)			
Δ from baseline#*	**+0.75±1.50**			**+2.00±3.54**			
Behavioural Inhibition System/Behavioural Activation System (BIS/BAS) Scales							
Drive Seeking (score/16)							
Baseline (*n*)	10.56±0.66 *(16)*	0.99	>0.99	11±0.67 (*14*)	0.16	0.36	
After treatment (*n*)	10.00±0.41 *(16)*	(-0.95 to	(-1.61 to	11.92±0.89 (*13*)	(-2.92 to	(-3.68 to	
Δ from baseline^	**+0.56±0.56**	2.08)	1.11)	**+1.08±0.73**	1.07)	1.48)	**0.08^**
Follow-up (*n*)	10.81±0.55 *(16)*			12.10±1.01 (*11*)			
Δ from baseline#*	**-0.25±0.50**			**+0.90±0.95**			
Fun Seeking (score/16)							
Baseline (*n*)	11.25±0.32 *(16)*	0.07	>0.99	11.1±0.5 (*14*)	0.16	0.61	
After treatment (*n*)	9.75±0.43 *(16)*	(-0.43 to	(-1.03 to	12.23±0.60 (*13*)	(-2.47 to	(-2.85 to	
Δ from baseline^	**-1.50±0.39**	2.57)	1.65)	**+1.00±0.51**	0.29)	1.34)	**0.05^**
Follow-up (*n*)	10.94±0.37 *(16)*			11.90±0.85 (*11*)			
Δ from baseline#*	**-0.31±0.49**			**+0.40±0.76**			
Reward Responsiveness (score/20)							
Baseline (*n*)	16.88±0.43 *(16)*	0.006**	>0.99	16.79±0.47 (*14*)	>0.99	0.75	
After treatment (*n*)	15.69±0.34 *(16)*	(0.33 to	(-0.78 to	16.69±0.63 (*13*)	(-1.29 to	(-1.58 to	
Δ from baseline^	**-1.19±0.31**	2.05)	1.53)	**0.00±0.51**	1.48)	1.75)	**0.47^**
Follow-up (*n*)	16.50±0.48 *(16)*			16.70±0.89 (*11*)			
Δ from baseline#*	**-0.38±0.42**			**-1.58±0.61**			

			BAS (score/28)				
Baseline (*n*)	20.56±0.88 *(16)*	>0.99	0.96	20.7±0.88 (*14*)	0.65	0.72	
After treatment (*n*)	20.31±1.04 *(16)*	(-1.15 to	(-1.02 to	21.23±0.97 (*13*)	(-1.92 to	(-1.97 to	
Δ from baseline^	**-0.25±0.52**	1.65)	2.27)	**+0.23±0.51**	0.89)	2.60)	**0.31^**
Follow-up (*n*)	19.94±1.11 *(16)*			20.40±1.34 (*11*)			
Δ from baseline#*	**-0.63±0.61**			**-0.30±0.82**			
			Hospital Anxiety and Depression Scale (HADS)				
			Anxiety (score/21)				
Baseline (*n*)	6.25±0.89 *(16)*	0.83	>0.99	7.43±1.2 (*14*)	0.86	0.14	
After treatment (*n*)	5.56±0.88 *(16)*	(-0.96 to	(-1.39 to	7.77±1.58 (*13*)	(-4.17 to	(-1.20 to	
Δ from baseline^	**-0.69±0.61**	2.33)	1.39)	**-0.23±1.37**	3.44)	4.52)	**0.74^**
Follow-up (*n*)	6.25±0.97 *(16)*			6.11±1.81 (*11*)			
Δ from baseline#*	**0.00±0.52**			**-1.44±0.88**			
			Depression (score/21)				
Baseline (*n*)	3.13±0.78 *(16)*	>0.99	0.73	6.57±0.95 (*14*)	0.28	0.08	
After treatment (*n*)	3.56±0.92 *(16)*	(-1.78 to	(-2.01 to	5.31±1.19 (*13*)	(-1.10 to	(-1.10 to	
Δ from baseline^	**+0.44±0.49**	0.91)	0.76)	**-1.31±1.17**	3.74)	3.74)	**0.15^**
Follow-up (*n*)	3.75±0.85 *(16)*			3.56±1.02 (*11*)			
Δ from baseline#*	**+0.63±0.51**			**-2.44±1.25**			
			Beck Depression Inventory				
			BDI-II (score/63)				
Baseline (*n*)	11.50±2.85 *(16)*	0.25	0.21	13.00±2.24 (*14*)	>0.99	>0.99	
After treatment (*n*)	9.56±2.29 *(16)*	(-0.88 to	(-1.09 to	12.00±3.00 (*13*)	(-10.29 to	(-12.32 to	
Δ from baseline^	**-1.9±1.05**	4.76)	6.59)	**-1.54±4.07**	22.95)	13.88)	**0.91^**
Follow-up (*n*)	8.75±2.68 *(16)*			12.22±4.02 (*11*)			
Δ from baseline#*	**-2.75±1.43**			**-2.78±4.62**			

			Behavioural changes				
			Alcohol Audit				
Baseline (*n*)	5.00±1.13 *(16)*	0.43	>0.99	2.57±0.66 (*14*)	0.26	0.31	
After treatment (*n*)	4.13±0.99 *(16)*	(-0.66 to	(-1.19 to	1.61±0.65 (*13*)	(-1.38 to	(-2.16 to	
Δ from baseline^	**-0.88±0.57**	2.41)	2.57)	**-1.00±3.08**	3.29)	4.11)	**0.90^**
Follow-up (*n*)	4.31±1.32 *(16)*			1.60±0.90 (*11*)			
Δ from baseline#*	**-0.69±0.69**			**-0.8±1.15**			

Data are displayed as mean±SEM (95% CI). The scores are based on set of questionnaires for GOP and RYGB at different time points**. 1-For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group at different time point performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value*[b], before treatment vs after treatment; ***P-value*[c], before treatment vs at follow-up). **2- For between groups comparisons** (GOP vs RYGB) of the averages of the changes from baseline; **Δ from baseline^** change from baseline at one-month on GOP or at three months post-RYGB**; Δ from baseline#**, change from baseline at follow-up (at two-month post GOP) or (at one-year after RYGB); ***P-value*[c] = difference in changes in treatment effect from baseline between groups (GOP vs RYGB) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for GOP) vs (Δ from baseline^ for RYGB) and # refer to the *P-value* of (Δ from baseline# for GOP) vs (Δ from baseline# for RYGB); *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001; Abbreviation: GOP, GLP-1 OXM 3-36PYY; RYGB, Roux-en-Y Gastric Bypass**; BIS/BAS,** Behavioural Inhibition System/Behavioural Activation Scale;, **HADS,** Hospital Anxiety and Depression Scale; **BDI-II,** Beck Depression Inventory.

5.5.3.4. Health-related quality of life following GOP

There was no significant improvement in health-related quality of life as measured by SF-36 and IWQoL post-GOP infusion.

5.5.3.4.1. SF-36TM health survey (SF-36) following infusion

GOP infusions did not result in significant changes in most areas of the eight domains that were measured using the SF-36 at any time point measured using RM One-Way **ANOVA**. There was also no significant difference from baseline in these domains observed between GOP and saline infusion apart from improvements in the energy/fatigue subscale one-month post saline compared to post GOP using unpaired t-test (P=0.02) (Table 21 on Page 199), and an improvement in physical functionality (P=0.02), limitations due to physical health (P=0.02), and general health (P=0.03) subscales in three-month post-RYGB (change from baseline measured using unpaired t-test) (Table 22 on Page 203).

5.5.3.4.2. Impact of Weight on Quality-of-Life Questionnaire (IWQoL-Lite) following the infusion

No significant changes from baseline were observed at any time point in all the domains of IWQoL-Lite post GOP, as compared to saline infusion, or RYGB measured using unpaired t-test (Table 21-22 on Page 199-206).

Table 21: *Quality-of-life following GOP/Saline*

Variables	**GOP** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**Saline** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**GOP vs. Saline** *P-value*[c]
			SF-36TM Health Survey (SF-36)				
			Physical Functioning (score/100)				
Baseline (*n*)	80.31±4.31 *(16)*	>0.99	>0.99	65.83±9.00 *(12)*	0.06	0.12	
After treatment (*n*)	81.88±3.47 *(16)*	(-10.06 to	(-9.92 to	74.58±7.96 *(12)*	(-18.12 to	(-13.84 to 1.3	**0.13**^
Δ from baseline^	**-1.56±3.12**	6.93)	14.29)	**+8.75±3.32**	0.62)		
Follow-up (*n*)	78.13±5.36 *(16)*			72.08±9.84 *(12)*			**0.15**[#]
Δ from baseline[#]*	**-2.19±4.49**			**+6.25±2.69**			
			Limitations due to physical health (score/100)				
Baseline (*n*)	76.56±8.68 *(16)*	0.86	>0.99	76.04±10.03 *(12)*	>0.99	>0.99	
After treatment (*n*)	84.38±8.50 *(16)*	(-26.98 to	(-27.98 to	81.25±11.15 *(12)*	(-28.76 to	(-11.58 to	**0.81**^
Δ from baseline^	**+7.81±7.12**	11.35)	24.86)	**+5.21±8.35**	18.35)	13.66)	
Follow-up (*n*)	78.13±7.86 *(16)*			75.00±11.10 *(12)*			**0.83**[#]
Δ from baseline[#]*	**+1.56±9.81**			**-1.04±4.48**			
			Limitations due to emotional problems (score/100)				
Baseline (*n*)	78.00±4.30 *(16)*	>0.99	>0.99	73.61±12.22 *(12)*	0.45	>0.99	
After treatment (*n*)	83.25±3.23 *(16)*	(-23.18 to	(-22.93 to	88.89±8.541 *(12)*	(-43.30 to	(-37.60 to	
Δ from baseline^	**+5.25±2.75**	23.18)	18.76)	**+15.28±9.94**	12.74)	45.94)	**0.53**^
Follow-up (*n*)	76.25±5.97 *(16)*			69.44±11.93 *(12)*			
Δ from baseline[#]*	**-1.75±2.85**			**-4.167±14.8**			**0.74**[#]
			Energy/Fatigue (score/100)				
Baseline (*n*)	54.06±6.17 *(16)*	0.12	>0.99	55.83±6.16 *(12)*	0.008**	0.22	
After treatment (*n*)	59.38±4.53 *(16)*	(-16.68 to	(-15.20 to	69.17±4.08 *(12)*	(-23.09 to	(-15.25 to	
Δ from baseline^	**+5.31±4.22**	6.05)	1.45)	**+13.33±3.46**	3.58)	2.74)	**0.02*^**
Follow-up (*n*)	60.94±5.72 *(16)*			62.08±5.72 *(12)*			
Δ from baseline[#]*	**+6.87±3.09**			**+6.25±3.19**			**0.77**[#]

			Emotional well-being (score/100)				
Baseline (*n*)	78.00±4.305 *(16)*	0.22	>0.99	79.33±4.79 *(12)*	>0.99	>0.99	
After treatment (*n*)	83.25±3.229 *(16)*	(-12.66 to	(-5.93 to	81.00±4.12 *(12)*	(-8.67 to	(-11.74 to	
Δ from baseline^	**+5.25±2.75**	2.16)	9.43)	**+1.7±2.48**	5.34)	13.07)	**0.39^**
Follow-up (*n*)	76.25±5.972 *(16)*			78.67±4.36 *(12)*			
Δ from baseline#	**-1.75±2.85**			**-0.67±4.39**			**0.83#**
			Social Functioning (score/100)				
Baseline (*n*)	78.91±6.52 *(16)*	0.04	>0.99	79.17±7.74 *(12)*	>0.99	0.57	
After treatment (*n*)	92.19±3.20 *(16)*	(-26.13 to -	(-13.93 to	85.42±5.51 *(12)*	(-30.21 to	(-18.90 to	**0.45^**
Δ from baseline^	**+13.28±4.77**	0.43)	9.25)	**+6.25±8.49**	17.71)	6.40)	
Follow-up (*n*)	81.25±5.47 *(16)*			85.42±4.57 *(12)*			**0.54#**
Δ from baseline#	**+2.34±4.30**			**+6.25±4.49**			
			Pain (score/100)				
Baseline (*n*)	75.63±5.55 *(16)*	0.24	>0.99	72.81±6.45 *(12)*	>0.99	>0.99	
After treatment (*n*)	82.34±5.17 *(16)*	(-16.45 to	(-6.88 to	75.00±6.73 *(12)*	(-16.14 to	(-14.64 to	
Δ from baseline^	**+6.71±3.61**	3.02)	14.04)	**+2.19±4.95**	11.77)	6.93)	**0.45^**
Follow-up (*n*)	72.03±6.03 *(16)*			76.67±6.17 *(12)*			
Δ from baseline#	**-3.59±3.87**			**+3.85±3.82**			**0.19#**
			General Health (score/100)				
Baseline (*n*)	60.32±4.30 *(16)*	>0.99	>0.99	54.17±5.35 *(12)*	>0.99	>0.99	
After treatment (*n*)	62.04±4.67 *(16)*	(-9.16 to	(-12.38 to	56.56±4.97 *(12)*	(-16.12 to	(-13.98 to	
Δ from baseline^	**+1.72±2.76**	5.72)	8.78)	**+2.39±4.87**	11.33)	7.53)	**0.89^**
Follow-up (*n*)	62.12±4.26 *(16)*			57.40±5.47 *(12)*			
Δ from baseline#	**+1.80±3.92**			**+3.23±3.81**			**0.80#**

			Impact of Weight on Quality of Life (IWQoL) on ***Physical Function (score/55)***				
Baseline (*n*)	24.50±2.17 *(16)*	.008**	0.52	23.58±2.51 *(12)*	0.04 *	0.0009 ***	
After treatment (*n*)	21.69±1.82 *(16)*	(0.69 to	(-1.78 to	21.67±2.84 *(12)*	(0.03 to	(1.57 to 5.27)	**0.41**^
Δ from baseline^	**-2.81±0.79**	4.93)	5.78)	**-1.92±0.67**	3.80)		
Follow-up (*n*)	22.50±1.96 *(16)*			20.17±2.33 *(12)*			**0.41**#
Δ from baseline#	**-2.00±1.40**			**-3.42±0.66**			
			Self-Esteem (score/35)				
Baseline (*n*)	21.38±2.05 *(16)*	>0.99	>0.99	18.21±1.75 *(12)*	>0.99	>0.99	
After treatment (*n*)	20.88±1.59 *(16)*	(-2.79 to	(-2.42 to	18.17±1.68 *(12)*	(-1.53 to	(-2.42 to	
Δ from baseline^	**-0.50±1.22**	3.79)	2.79)	**-0.04±0.56**	1.62)	3.01)	**0.76**
Follow-up (*n*)	21.19±1.79 *(16)*			17.92±1.69 *(12)*			
Δ from baseline#	**-0.188±0.97**			**-0.29±0.96**			**0.94**#
			Sexual Life (score/20)				
Baseline (*n*)	7.75±0.75 *(16)*	>0.99	>0.99	8.38±1.23 *(12)*	>0.99	0.81	
After treatment (*n*)	8.06±0.87 *(16)*	(-1.84 to	(-2.31 to	8.75±1.37 *(12)*	(-1.89 to	(-1.14 to	
Δ from baseline^	**+0.31±0.57**	1.22)	1.31)	**+0.38±0.54**	1.15)	2.72)	**0.93**^
Follow-up (*n*)	8.25±0.83 *(16)*			7.58±1.39 *(12)*			
Δ from baseline#	**-0.50±0.67**			**-0.79±0.68**			**0.19**#
			Public Distress (score/25)				
Baseline (*n*)	10.75±1.39 *(16)*	>0.99	>0.99	10.00±1.67 *(12)*	>0.99	0.08	
After treatment (*n*)	10.38±1.06 *(16)*	(-0.99 to	(-1.98 to	9.75±1.64 *(12)*	(-1.13 to	(-0.18 to	**0.86**^
Δ from baseline^	**-0.38±0.51**	1.74)	1.98)	-0**.25±0.49**	1.63)	3.17)	
Follow-up (*n*)	10.75±1.29 *(16)*			8.500±1.40 *(12)*			**0.14**#
Δ from baseline#	**0.00±0.74**			**-1.50±0.59**			
			Work Problems (score/20)				
Baseline (*n*)	7.625±0.65 *(16)*	0.23	>0.99	7.08±1.01 *(12)*	0.25	0.54	
After treatment (*n*)	6.625±0.60 *(16)*	(-0.44 to	(-1.45 to	6.17±0.76 *(12)*	(-0.45 to	(-0.65 to	
Δ from baseline^	**-1.00±0.53**	2.43)	1.95)	**-0.92±0.48**	2.28)	1.98)	**0.91**^
Follow-up (*n*)	7.38±0.85 *(16)*			6.42±0.78 *(12)*			
Δ from baseline#	**-0.25± 0.63**			**-0.67±0.47**			**0.62**#

IWQoL Total (score/155)							
Baseline (*n*)	72.00±5.89 *(16)*	0.35	>0.99	67.25±6.67 *(12)*	0.16	0.04*	
After treatment (*n*)	67.63±4.87 *(16)*	(-2.73 to	(-6.57 to	64.50±6.63 *(12)*	(-0.86 to	(0.16 to	
Δ from baseline^	**-4.38±2.64**	11.48)	10.44)	**-2.75±1.28**	6.36)	13.17)	**0.62^**
Follow-up (*n*)	70.06±5.47 *(16)*			60.58±5.68 *(12)*			
Δ from baseline#	**-1.94±3.16**			**-6.67±2.30**			**0.26#**

Data are displayed as **mean±SEM** (95% CI). The scores are based on set of questionnaires at baseline, one-month on infusion (after treatment), and two-month post the infusion (follow-up). **1- For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value*** [a], before treatment vs after treatment; ***P-value*** [b], before treatment vs at follow-up). **2- For between groups comparisons** (GOP vs Saline) of the averages of the changes from baseline; **Δ from baseline^**, change from baseline at one-month on the infusion**; Δ from baseline#**, change from baseline at follow-up (two-month post the infusion); ***P-value*** [c] = difference in changes in treatment effect from baseline between groups (GOP vs Saline) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for GOP) vs (Δ from baseline^ for Saline) at one-month of infusion and # refer to the *P-value* of (Δ from baseline# for GOP) vs (Δ from baseline# for Saline) at two-month post-infusion. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. Abbreviation: GOP, GLP-1 OXM 3-36PYY; IWQoL, Impact of Weight on Quality of Life.

Table 22: *Quality-of-life following GOP/RYGB*

Variables	**GOP** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**RYGB** Mean±SEM	*P-value* [a] (95% CI)	*P-value*[b] (95% CI)	**GOP vs. RYGB** *P-value*[c]
SF-36TM Health Survey (SF-36)							
Physical Functioning (score/100)							
Baseline (*n*)	80.31±4.31 *(16)*	>0.99 (-10.06 to 6.93)	>0.99 (-9.92 to 14.29)	48.9±7.76 (*14*)	0.056 (-50.45 to 0.61)	0.0002 *** (-57.37 to -24.77)	**0.02*^**
After treatment (*n*)	81.88±3.47 *(16)*			73.85±7.14 (*13*)			
Δ from baseline^	**+1.56±3.12**			**+23.46±9.34**			
Follow-up (*n*)	78.13±5.36 *(16)*			90.00±4.17 (*11*)			
Δ from baseline[#]*	**-2.19±4.49**			**+40.00±5.95**			
Limitations due to physical health (score/100)							
Baseline (*n*)	76.56±8.68 *(16)*	0.86 (-26.98 to 11.35)	>0.99 (-27.98 to 24.86)	53.57±11.68 (*14*)	0.007** (-27.20 to -9.12)	0.062 (-77.78 to 1.59)	**0.02*^**
After treatment (*n*)	84.38±8.50 *(16)*			94.23±4.15 (*13*)			
Δ from baseline^	**+7.81±7.12**			**+38.46±11.54**			
Follow-up (*n*)	78.13±7.86 *(16)*			91.67±8.33 (*11*)			
Δ from baseline[#]*	**+1.56±9.81**			**+36.11±14.50**			
Limitations due to emotional problems (score/100)							
Baseline (*n*)	78.00±4.30 *(16)*	>0.99 (-23.18 to 23.18)	>0.99 (-22.93 to 18.76)	61.9±10 (*14*)	0.055 (-49.11 to 3.69)	0.040* (-75.90 to 7.12)	**0.28^**
After treatment (*n*)	83.25±3.23 *(16)*			84.62±8.10 (*13*)			
Δ from baseline^	**+5.25±2.75**			**+20.51±9.65**			
Follow-up (*n*)	76.25±5.97 *(16)*			96.30±3.70 (*11*)			
Δ from baseline[#]*	**-1.75±2.85**			**+37.04±15.16**			
Energy/Fatigue (score/100)							
Baseline (*n*)	54.06±6.18 *(16)*	0.12 (-16.68 to 6.05)	>0.99 (-15.20 to 1.45)	47.86±4.96 (*14*)	0.46 (-28.07 to 16.09)	0.144 (-34.88 to 8.37)	**0.55^**
After treatment (*n*)	59.38±4.54 *(16)*			53.85±6.33 (*13*)			
Δ from baseline^	**+5.31±4.22**			**+6.15±8.09**			
Follow-up (*n*)	60.94±5.72 *(16)*			61.11±7.10 (*11*)			
Δ from baseline[#]*	**+6.87±3.09**			**+12.78±7.91**			

			Emotional well-being (score/100)				
Baseline (*n*)	78.00±4.30 *(16)*	0.22 (-12.66 to 2.16)	>0.99 (-5.93 to 9.43)	70.86±5.2 (*14*)	0.29 (-7.67 to 21.38)	0.072 (-14.69 to -0.03)	**0.06^**
After treatment (*n*)	83.25±3.23 *(16)*			64.00±7.71 (*13*)			
Δ from baseline^	**+5.25±2.75**			**-5.85±5.31**			
Follow-up (*n*)	76.25±5.97 *(16)*			78.22±7.15 (*11*)			
Δ from baseline#	**-1.75±2.85**			**+5.33±2.58**			
			Social Functioning (score/100)				
Baseline (*n*)	78.91±6.52 *(16)*	0.04 (-26.13 to -0.43)	>0.99 (-13.93 to 9.25)	62.3±7.9 (*14*)	0.63 (-34.72 to 20.90)	0.028* (-50.35 to -5.56)	**0.43^**
After treatment (*n*)	92.19±3.20 *(16)*			69.23±7.96 (*13*)			
Δ from baseline^	**+13.28±4.77**			**+5.00±10.17**			
Follow-up (*n*)	81.25±5.47 *(16)*			90.28±4.55 (*11*)			
Δ from baseline#	**+2.34±4.30**			**+20.83±7.79**			
			Pain (score/100)				
Baseline (*n*)	75.63±5.55 *(16)*	0.24 (-16.45 to 3.02)	>0.99 (-6.88 to 14.04)	54.8±5.8 (*14*)	0.015* (-45.49 to -1.40)	0.001** (-48.18 to -12.74)	**0.06^**
After treatment (*n*)	82.34±5.17 *(16)*			78.27±4.44 (*13*)			
Δ from baseline^	**+6.71±3.61**			**+22.69±8.07**			
Follow-up (*n*)	72.03±6.03 *(16)*			85.28±5.58 (*11*)			
Δ from baseline#	**-3.59±3.87**			**+30.83±8.07**			
			General Health (score/100)				
Baseline (*n*)	60.32±4.30 *(16)*	>0.99 (-9.16 to 5.72)	>0.99 (-12.38 to 8.78)	48.39±6.34 (*14*)	0.02* (-27.94 to 2.23)	0.112 (-41.23 to 5.51)	**0.03^**
After treatment (*n*)	62.04±4.67 *(16)*			61.25±6.01 (*13*)			
Δ from baseline^	**+1.72±2.76**			**+14.42±5.51**			
Follow-up (*n*)	62.12±4.26 *(16)*			66.25±8.00 (*11*)			
Δ from baseline#	**+1.80±3.92**			**+15.14±8.49**			
			Impact of Weight on Quality of Life (IWQoL) on				
Physical Function (score/55)							
Baseline (*n*)	24.50±2.17 *(16)*	0.008** (0.69 to 4.93)	0.52 (-1.78 to 5.78)	32.57±3.5 (*14*)	0.012* (1.87 to 16.35)	0.061 (-0.55 to 26.36)	**0.06^**
After treatment (*n*)	21.69±1.82 *(16)*			23.46±2.96 (*13*)			
Δ from baseline^	**-2.81±0.79**			**-7.69±2.62**			
Follow-up (*n*)	22.50±1.96 *(16)*			19.67±4.15 (*11*)			
Δ from baseline#	**-2.00±1.40**			**-10.56±4.58**			

Self-Esteem (score/35)							
Baseline (*n*)	21.38±2.05 *(16)*	>0.99	>0.99	23.79±2.3 (*14*)	0.158	0.068	
After treatment (*n*)	20.88±1.59 *(16)*	(-2.79 to	(-2.42 to	21.00±2.82 (*13*)	(-3.67 to	(1.24 to	
Δ from baseline^	**-0.50±1.22**	3.79)	2.79)	**-3.54±2.35**	9.24)	14.33)	**0.23^**
Follow-up (*n*)	21.19±1.79 *(16)*			16.00±3.29 (*11*)			
Δ from baseline#	**-0.188±0.97**			**-4.33±2.06**			
Sexual Life (score/20)							
Baseline (*n*)	7.75±0.75 *(16)*	>0.99	>0.99	13.01±1.2 (*14*)	0.232	0.037*	
After treatment (*n*)	8.06±0.87 *(16)*	(-1.84 to	(-2.31 to	10.77±1.66 (*13*)	(-3.04 to	(-0.87 to	
Δ from baseline^	**+0.31±0.57**	1.22)	1.31)	**-2.46±1.96**	7.64)	10.12)	**0.14^**
Follow-up (*n*)	8.25±0.83 *(16)*			8.44±1.22 (*11*)			
Δ from baseline#	**+0.50±0.67**			**-5.00±1.96**			
Public Distress (score/25)							
Baseline (*n*)	10.75±1.39 *(16)*	>0.99	>0.99	14.57±1.5 (*14*)	0.417	0.074	
After treatment (*n*)	10.38±1.06 *(16)*	(-0.99 to	(-1.98 to	13.00±2.14 (*13*)	(-1.95 to	(-1.07 to	
Δ from baseline^	**-0.38±0.51**	1.74)	1.98)	**-1.08±1.28**	5.09)	10.21)	**0.58^**
Follow-up (*n*)	10.75±1.29 *(16)*			10.00±1.95 (*11*)			
Δ from baseline#	**0.00±0.74**			**-4.22±2.06**			
Work Problems (score/20)							
Baseline (*n*)	7.625±0.65 *(16)*	0.23	>0.99	9.85±1.07 (*14*)	0.371	0.078	
After treatment (*n*)	6.625±0.60 *(16)*	(-0.44 to	(-1.45 to	9.15±1.54 (*13*)	(-1.33 to	(-0.41 to	
Δ from baseline^	**-1.00±0.53**	2.43)	1.95)	**-0.69±0.75**	2.74)	5.68)	**0.73^**
Follow-up (*n*)	7.38±0.85 *(16)*			7.22±1.26 (*11*)			
Δ from baseline#	**-0.25± 0.63**			**-2.22±1.10**			

IWQoL Total (score/155)							
Baseline (*n*)	72.00±5.89 *(16)*	0.35 (-2.73 to 11.48)	>0.99 (-6.57 to 10.44)	94.57±60 (*14*)	0.021* (0.48 to 33.89)	0.008** (11.09 to 55.39)	**0.06**^
After treatment (*n*)	67.63±4.87 *(16)*			77.38±10.10 (*13*)			
Δ from baseline^	**-4.38±2.64**			**-16.23±6.11**			
Follow-up (*n*)	70.06±5.47 *(16)*			61.33±9.94 (*11*)			
Δ from baseline#	**-1.94±3.16**			**-27.44±7.84**			

Data are displayed as mean±SEM (95% CI). The scores are based on set of questionnaires for GOP and RYGB at different time points**. 1-For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group at different time point performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value*[a], before treatment vs after treatment; ***P-value*[b], before treatment vs at follow-up). **2- For between groups comparisons** (GOP vs RYGB) of the averages of the changes from baseline; **Δ from baseline^** change from baseline at one-month on GOP or at three months post-RYGB**; Δ from baseline#**, change from baseline at follow-up (at two-month post GOP) or (at one-year after RYGB); ***P-value*[c] = difference in changes in treatment effect from baseline between groups (GOP vs RYGB) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for GOP) vs (Δ from baseline^ for RYGB) and # refer to the *P-value* of (Δ from baseline# for GOP) vs (Δ from baseline# for RYGB); *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001; Abbreviation: GOP, GLP-1 OXM 3-36PYY; RYGB, Roux-en-Y Gastric Bypass**;** IWQoL, Impact of Weight on Quality of Life

5.5.4. Changes in food intake based on dietary records following GOP infusion

Changes in energy intake during the infusion were investigated using a four-day food diary. No significant difference at baseline in food and alcohol consumption or micronutrient composition between the groups studied was observed at baseline using a mixed-effects model with a Bonferroni post hoc test (Table 23 on Page 208). In the infusion groups, 16 and 12 participants in GOP and saline respectively completed the 4-day food diary at baseline, after one-month on the infusion, and two-month after completing the infusion. The GOP group at one-month was then compared to the RYGB surgery group at three months post-surgery (n=16). Total caloric intake per day was significantly reduced one-month on GOP infusion compared to baseline (overall P=0.006) using RM One-way **ANOVA** with multiple comparisons and a Bonferroni post hoc test (Adjusted P=0.004). The participants consumed 735.6±187.1 kcal/day less per day compared to baseline (2073±188.2 kcal/day). Although the intake increased two-month after completing the infusion to 1726±190.3 kcal/day compared to the intake during GOP (1338±96.95 kcal/day), it remained lower than the baseline intake. In the control group, there was a reduction in food consumption of 437.3±173.3 kcal/day, but this reduction did not reach a significant level at any time point (overall P=0.082) (Table 24 on Page 209). There was no significant change in macronutrient composition post-GOP infusion at any point. In comparison to RYGB, the mean percentage of carbohydrate consumption in the GOP group was 4.21±2.15% lower and fat percentage was 1.33±2.13% higher during one-month on the GOP infusion compared to three-month post-RYGB (+3.08±2.59% and -6.59±2.14% respectively, P=0.04 and P=0.01 respectively) (Table 25 on Page 211).

***Table** 23: Baseline food intake data across all intervention groups*

GOP N=16	**Saline N=12**	**RYGB N=16**
Total energy intake (Kcal/day)		
2073±188.2	2134±199.3	1883±141
Macronutrient composition		
Carbohydrates (% total kcal intake)		
41.9±2	37.29±2	43±2
Protein (% total kcal intake)		
18.14±0.8	18.1±1	39±2
Fat (% total kcal intake)		
37.31±1.4	41.84±1.9	17±1
Alcohol intake (% total kcal intake)		
2.7±0.00	2.8±1.1	0.4±0.4

Data are presented as mean±SEM (95% CI). One-way ANOVA applied for comparison between groups. Abbreviations: GOP, GLP-1 OXM 3-36PYY; RYGB, Roux-en-Y Gastric Bypass.

Table 24: *Changes in food, alcohol and macronutrient composition intake following GOP/Saline*

Variables	**GOP** Mean±SEM	*P-value*[a] (95% CI)	*P-value*[b] (95% CI)	**Saline** Mean±SEM	*P-value*[a] (95% CI)	*P-value*[b] (95% CI)	**GOP vs. Saline** *P-value*[c]
Total energy intake (kcal/day)							
Baseline (*n*)	2073±188.2 *(16)*	0.004**	0.448	2134±199.3 (*12*)	0.22	0.12	
After treatment (*n*)	1338±96.95 *(16)*	(192.5 to 1279)	(-243.5 to 937.3)	1697±160 (*12*)	(-163.4 to 1038)	(-102.9 to 1163)	
Δ from baseline^	**-735.6±187.1**			**-437.3±173.3**			**0.27**^
Follow-up (*n*)	1726±190.3 *(16)*			1604±138.6 (*12*)			
Δ from baseline[#]	**-459.2±186.8**			**-551.9±191.5**			**0.73**[#]
Macronutrient composition							
Carbohydrates (% total kcal intake)							
Baseline (*n*)	41.9±2.00 *(16)*	0.44	>0.99	37.29±2.00 (*12*)	>0.99	0.17	
After treatment (*n*)	37.8±1.80 *(16)*	(-2.85 to 10.98)	(-5.82 to 9.07)	35.54±2.70 (*12*)	(-6.07 to 9.56)	(-14.66 to 1.85)	
Δ from baseline^	**-4.21±2.15**			**-2.30±2.77**			**0.58**^
Follow-up (*n*)	40.25±2.20 *(16)*			43.7±1.40 (*12*)			
Δ from baseline[#]	**-1.65±0.79**			**+5.59±3.14**			**0.01**[#]
Protein (% total kcal intake)							
Baseline (*n*)	18.14±0.80 *(16)*	0.47	0.62	18.1±1.00 (*12*)	0.37	>0.99	
After treatment (*n*)	20.00±1.00 *(16)*	(-5.12 to 1.39)	(-5.30 to 1.71)	20.13±0.70 (*12*)	(-5.4 to 1.27)	(-4.79 to 2.30)	
Δ from baseline^	**+2.28±1.43**			**+2.84±1.23**			**0.77**^
Follow-up (*n*)	19.93±0.70 *(16)*			19.3±0.9 (*12*)			
Δ from baseline[#]	**+1.97±2.25**			**+1.73±1.39**			**0.53**[#]
Fat (% total kcal intake)							
Baseline (*n*)	37.31±1.40 *(16)*	>0.99	>0.99	41.84±1.9 (*12*)	>0.99	0.03	
After treatment (*n*)	39.11±1.70 *(16)*	(-7.45 to 3.85)	(-6.31 to 5.86)	42.58±2.4 (*12*)	(-7.77 to 6.29)	(0.36 to 15.22)	
Δ from baseline^	**+1.33±2.13**			**+0.79±2.27**			**0.86**^
Follow-up (*n*)	37.54±1.90 *(16)*			34.05±1.40 (*12*)			
Δ from baseline[#]	**+1.97±2.25**			**-7.22±2.15**			**0.009**[#]**

			Alcohol (% total kcal intake)				
Baseline (*n*)	2.70±1.00 *(16)*	>0.99	>0.99	2.80±1.10 (*12)*	>0.99	>0.99	
After treatment (*n*)	3.075±1.50 *(16)*	(-4.68 to 3.89)	(-4.23 to 5.02)	1.75±0.95 (*12)*	(-2.69 to 4.84)	(-4.13 to 3.84)	
Δ from baseline^	**+0.60±1.90**			**-1.33±0.89**			**0.41^**
Follow-up (*n*)	2.27±1.00 *(16)*			2.97±1.26 (*12)*			
Δ from baseline#	**-0.78±1.46**			**-0.10±0.95**			**0.71#**

Data are displayed as **mean±SEM** (95% CI). The scores are based on set of questionnaires at baseline, one-month on infusion (after treatment), and two-month post the infusion (follow-up). **1- For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value*** [a], before treatment vs after treatment; ***P-value*** [b], before treatment vs at follow-up). **2- For between groups comparisons** (GOP vs Saline) of the averages of the changes from baseline; **Δ from baseline^**, change from baseline at one-month on the infusion**; Δ from baseline#**, change from baseline at follow-up (two-month post the infusion); ***P-value*** [c] = difference in changes in treatment effect from baseline between groups (GOP vs Saline) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for GOP) vs (Δ from baseline^ for Saline) at one-month of infusion and # refer to the *P-value* of (Δ from baseline# for GOP) vs (Δ from baseline# for Saline) at two-month post-infusion. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. Abbreviation: GOP, GLP-1 OXM 3-36PYY

Table 25: *Changes in food, alcohol and macronutrient composition intake following GOP/RYGB*

Variables	**GOP** Mean±SEM	*P-value*[a] (95% CI)	*P-value*[b] (95% CI)	**RYGB** Mean±SEM	*P-value*[a] (95% CI)	*P-value*[b] (95% CI)	**GOP vs. RYGB** *P-value*[c]
Total energy intake (kcal/day)							
Baseline (*n*)	2073±188.2 *(16)*	0.004**	0.448	1883±141 *(14)*	<0.0001	0.0031	
After treatment (*n*)	1338±96.95 *(16)*	(192.5 to 1279)	(-243.5 to 937.3)	937.0±92.79 *(13)*	(385.0 to 1361)	(322.7 to 1029)	
Δ from baseline^	**-735.6±187.1**			**-945.6±135.5**			**0.36^**
Follow-up (*n*)	1726±190.3 *(16)*			1207±145 *(11)*			
Δ from baseline#	**-459.2±186.8**			**-676±4**			
Macronutrient composition							
Carbohydrates (% total kcal intake)							
Baseline (*n*)	41.9±2.00 *(16)*	0.44	>0.99	43.85±1.57 *(14)*	>0.99	>0.99	
After treatment (*n*)	37.8±1.80 *(16)*	(-2.85 to 10.98)	(-5.82 to 9.07)	46.8±2.7 *(13)*	(-10.68 to	(-9.35 to 8.27)	
Δ from baseline^	**-4.21±2.15**			**+3.08±2.59**	4.77)		**0.04*^**
Follow-up (*n*)	40.25±2.2 *(16)*			44.40±2.55 *(11)*			
Δ from baseline#	**-1.65±0.79**			-0.55			
Protein (% total kcal intake)							
Baseline (*n*)	18.14±0.80 *(16)*	0.47	0.62	16.84±0.70 *(14)*	0.01*	0.26	
After treatment (*n*)	20.00±1.00 *(16)*	(-5.12 to 1.39)	(-5.30 to 1.71)	20.9±1.20 *(13)*	(-7.40 to -0.68)	(-6.51 to 1.15)	
Δ from baseline^	**+2.28±1.43**			**+4.04±1.23**			**0.35^**
Follow-up (*n*)	19.93±0.70 *(16)*			19.53±1.15 *(11)*			
Δ from baseline#	**+1.97±2.25**			-2.69			
Fat (% total kcal intake)							
Baseline (*n*)	37.31±1.40 *(16)*	>0.99	>0.99	38.9±1.7 *(14)*	0.10	0.64	
After treatment (*n*)	39.11±1.7 *(16)*	(-7.45 to 3.85)	(-6.31 to 5.86)	32.3±2.5 *(13)*	(-0.92 to	(-4.24 to 12.87)	
Δ from baseline^	**+1.33±2.13**			**+6.59±2.14**	14.09)		**0.01*^**
Follow-up (*n*)	37.54±1.9 *(16)*			34.58±2.49 *(11)*			
Δ from baseline#	**+1.97±2.25**			**-5.32**			

			Alcohol (% total kcal intake)				
Baseline (*n*)	2.70±1.00 *(16)*	>0.99	>0.99	0.4±0.4 *(14)*	>0.99	0.47	
After treatment (*n*)	3.075±1.5 *(16)*	(-4.68 to 3.89)	(-4.23 to 5.02)	0.00 *(13)*	(-1.24 to 2.07)	(-2.97 to 0.79)	
Δ from baseline^	**+0.60±1.90**			**-0.42±0.36**			**0.59^**
Follow-up (*n*)	2.27±1.00 *(16)*			0.00 *(11)*			
Δ from baseline#	**-0.78±1.46**			**0.00**			

Data are displayed as mean±SEM (95% CI). The scores are based on set of questionnaires for GOP and RYGB at different time points**. 1-For within group comparisons** of each intervention (before vs after); The comparison of averages of absolute scores within the group at different time point performed by using RM One-way ANOVA with correcting for multiple comparisons using Bonferroni post hoc test (adjusted P-value = ***P-value*[a], before treatment vs after treatment; ***P-value*[b], before treatment vs at follow-up). **2- For between groups comparisons** (GOP vs RYGB) of the averages of the changes from baseline; **Δ from baseline^** change from baseline at one-month on GOP or at three months post-RYGB**; Δ from baseline#**, change from baseline at follow-up (at two-month post GOP) or (at one-year after RYGB); ***P-value*[c] = difference in changes in treatment effect from baseline between groups (GOP vs RYGB) performed by using a Student Unpaired t-test where ^ refer to the *P-value* of (Δ from baseline^ for GOP) vs (Δ from baseline^ for RYGB) and # refer to the *P-value* of (Δ from baseline# for GOP) vs (Δ from baseline# for RYGB); *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001; Abbreviation: GOP, GLP-1 OXM 3-36PYY; RYGB, Roux-en-Y Gastric Bypass

5.5.5. Anthropometric data following GOP infusion

After one-month of GOP infusion, mean body weight had dropped significantly in comparison to baseline at the two measured time points (P<0.0001, RM one-Way **ANOVA** with a Bonferroni post-hoc test). The mean weight loss at one-month was 4.2±0.5 kg, -4.0±0.4% (Table 26 on Page 214). Although the saline group also lost a significant amount of weight at one-month in comparison to baseline (-2.5±0.7kg, -2.0±0.6%), a significantly higher reduction in bodyweight was observed in the GOP infusion group (-4.0±0.4%) in comparison to the saline group (-2.0±0.6%) (P=0.001, unpaired t-test) (Table 27 on Page 215). For the RYGB results, the data reflecting weight loss following one-month of GOP infusion were significantly less than the weight loss three months post-RYGB (-4.0±0.4% vs -17.82±1.10% respectively, P<0.0001, unpaired t-test) (different timeframe). See Table 26-27 on page 214-215; Figure 9 on page 216).

Table 26: *Changes in body weight across interventions*

GOP N=16	**Baseline**	**One-month**	**Two-month**	*P-value*[a] (95% CI)	*P-value*[b] (95% CI)
Weight (kg)	111.5±6.5	107±6.5	109±6.6	<0.0001 (3.08 to 5.44)	0.028 (0.15 to 4.76)
BMI (kg/m^2)	38.5±1.6	36.8±1.6	37.5±1.6	<0.0001 (1.19 to 2.02)	0.015 (0.17 to 1.69)
Saline N=12	**Baseline**	**One-month**	**Two-month**	*P-value*[a] (95% CI)	*P-value*[b] (95% CI)
Weight (kg)	119.1±6.9	116.8±6.6	116.9±6.7	0.019 (0.189 to 4.24)	0.342 (-1.43 to 5.86)
BMI (kg/m^2)	39.5±1.5	38.7±1.5	38.8±1.6	0.015 (0.138 to 1.33)	0.303 (-0.39 to 0.62)
RYGB	**Baseline**	**Three months**	**One-year**	*P-value*[a] (95% CI)	*P-value*[b] (95% CI)
N	14	13	11	Pre vs. Three-month	Pre vs. One-year
Weight (kg)	116.6±6.9	97.55±5.9	75.09±4.1	<0.0001 (13.57 to 24.60)	<0.0001 (30.24 to 52.85)
BMI (kg/m^2)	42.4+1.6	32.76±2.9	22.57±3.43	<0.0001 (5.66 to 8.53)	<0.0001 (10.87 to 16.42)

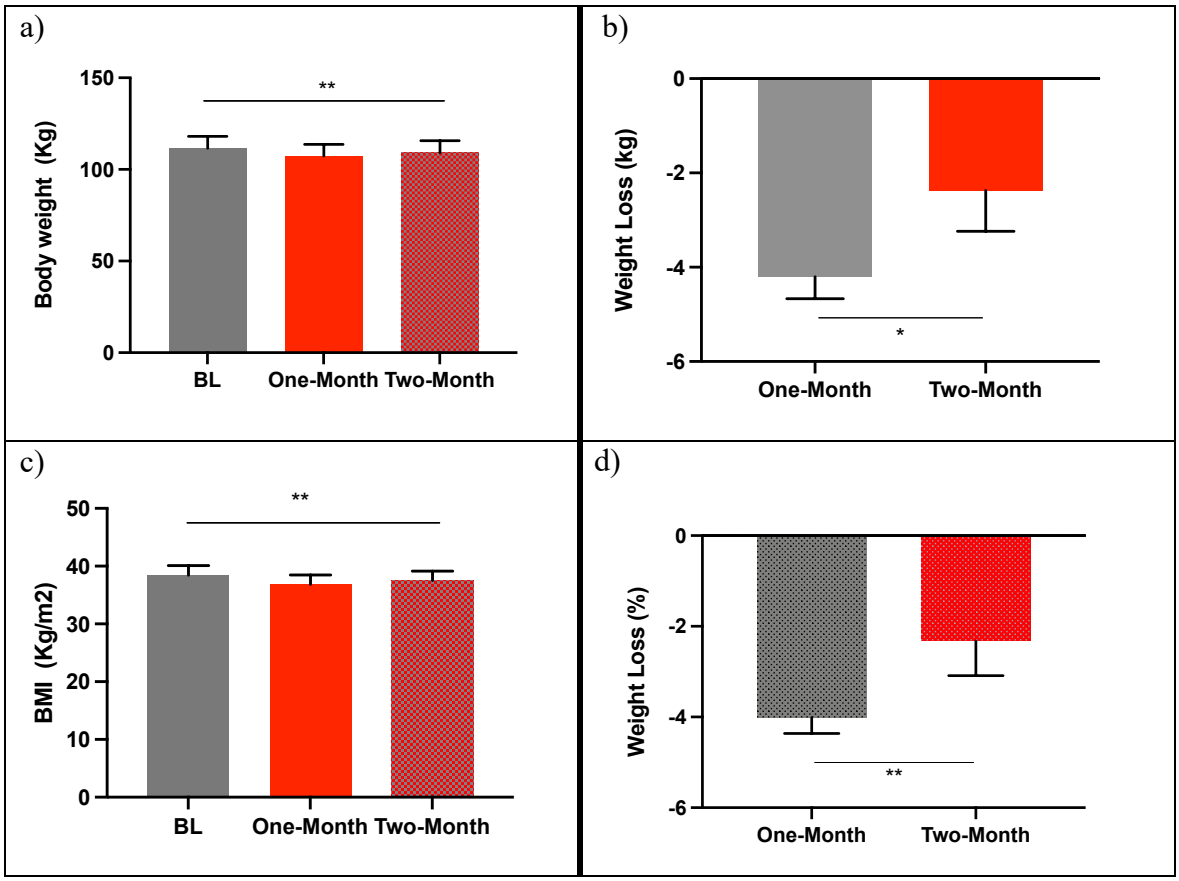
Data are displayed as mean±SEM (95% CI) for bodyweight at baseline, and multiple time-points for GOP, saline (one-month during and two-month post-infusion), and RYGB group (three months, and one-year after surgery). For primary comparison (within-group comparison), analysis was performed using one-Way ANOVA for the comparison of averages bodyweight between different time points) with correction for multiple comparisons using a Bonferroni post-hoc test (adjusted P.value; P-value[a], baseline vs one-month post infusion (GOP or saline) or baseline vs three-month post-RYGB and P-value[b], baseline vs two-month post infusion or baseline vs one-year post-RYGB).

Table 27: *Change in percentage body weight across interventions*

	GOP N=16			**GOP vs Saline *P-value*[b]**	
	One-month	**Two-month**	***P-value*[a]**	**One-month**	**Two-month**
WL (kg)	-4.2±0.5	-2.4±0.9	0.010 *	0.007	0.831
%WL	-4.0±0.4	-2.2±0.8	0.004 **	0.001 **	0.598
	Saline N=12			**GOP vs RYGB *P-value*[b]**	
	One-month	**Two-month**	***P-value*[a]**		
WL (kg)	-2.5±0.7	-2.5±0.7	-2.5±0.7		
%WL	-2.0±0.6	-2.0±0.6	-2.0±0.6		
	RYGB			**One-month of GOP vs three-month post-RYGB**	
	Three months	**One-year**	***P-value*[a]**		
	N=13	**N=11**			
WL (kg)	-21.25±1.9	-32.45±3	<0.0001	<0.0001	
%WL	-17.82±1.10	-29.69±1.45	<0.0001	<0.0001	

Data are displayed as mean±SEM (95% CI) for percentage weight loss at baseline, and multiple time-points for GOP, saline (one-month during and two-month post-infusion), and RYGB group (three months, and one-year post surgery). For secondary comparison of (1)-time effect after each treatment between groups, a Student Paired t-test was preformed (P-value[a]), (2) for a comparison of treatment effect between the GOP and Saline arms a student Unpaired t-test was preformed (P-value[b]). *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

Figure 9: *Effects of GOP on body weight and BMI throughout the study*



Data are presented as mean±SEM at one-month and three months. A) A significant reduction in the absolute BW (kg) using a mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test. b) Weight loss in kg using a Student Paired t-test at one-month on a GOP and two-month post-GOP. C) Percentage weight loss post-GOP (%) using Student Paired t-test. d) A significant reduction in BMI (kg/m^2) using mixed-effects model with correction for multiple comparisons using Bonferroni's post hoc test. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

5.6. Discussion

5.6.1. Summary of the infusion group findings

This prospective single-blind observational study was aimed at examining the results of a chronic subcutaneous infusion of GOP on eating behaviour, food rewards, psychological wellbeing and health-related quality of life of patients living with obesity and T2DM. The study used validated questionnaires to compare results with those of a control group whose members received a saline infusion. The GOP group was also compared to patients who had undergone RYGB surgery three months previously. Food consumption was measured using a 4-day food diary and was also assessed across all interventions.

The only change observed in eating behaviour following one-month on GOP was in dietary restraint score, as measured by DEBQ, in which the increase in restraint was sustained for up to two-month after the infusion. This increase was also significantly observed three months postoperatively. Interestingly, when the change from baseline was compared, GOP and RYGB had a similar impact on dietary restraint at one-month and three months post-RYGB respectively. The change from baseline in reward food intake was statistically superior to the RYGB group in comparison to GOP. Psychologically, there was a significant reduction at one-month after GOP infusion in BAS fun-seeking, which is related to impulsivity and similar to sensation seeking. There was a non-significant trend in the reduction from baseline in fun-seeking behaviour after one-month on the GOP infusion in comparison to three months after RYGB. There was no significant impact of GOP infusion on alcohol consumption. Meanwhile, when comparing changes from baseline between GOP vs RYGB, and GOP vs Saline, all the interventions were similar, showing no significant impact on emotional eating, hunger, eating concerns, depression, and anxiety, impulsivity and alcohol consumption. In terms of food intake, data showed a reduction in daily intake of 736 kcal/day, with no changes in macronutrient compositions after one-month of GOP infusion. Food intake three months after

RYGB was down by 945.6±135.5 kcal/day. This reduction was not significantly different to the post-GOP reduction. However, the change from baseline in the percentage of carbohydrate consumption was significantly lower in the GOP group at one-month in comparison with the RYGB figures at three months after surgery, while the fat consumption was significantly lower in the surgical group in comparison to the GOP group.

5.6.2. Reward drive to eat and food intake following GOP infusion

Pleasure-based eating, particularly in the modern food environment, offers many opportunities for overeating, encouraging weight gain and obesity. The drive to consume food for pleasure has been referred to as hedonic hunger (406), which can be measured using the power of food scale (PFS) (287). This scale does not quantify preferences or actual food intake, although it does predict a preoccupation with palatable foods (427). Evidence suggests that higher PFS scores are correlated with increased levels of daily snacking (582). The results of the current study show that chronic infusion of GOP, as assessed by the PFS, did not reduce the reward value of food to the extent observed after RYGB. To the best of my knowledge, no study has so far been conducted to examine the impact of GOP hormones on the reward drive to eat using the PFS. However, fMRI studies support the role of satiety gut hormones in altering reward responses. In one study, the combined administration of GLP-1 and PYY to fasting participants without obesity mimicked the effect of the brain's reward activity as observed physiologically after eating, resulting in a reduction in *ad libitum* food intake during buffet meals (196).

In another fMRI study, PYY was infused intravenously to mimic the full state. There was an increase in the resting activity of the reward system in the brain (regions like the orbital frontal cortex) in relation to food reward when compared to the saline infusion, and this was used to predict subsequent consumption behaviour. The authors suggested that the reward value of food is diminished by PYY modification of the **OFC** (583). However, as well as the surge in

GOP hormones following RYGB surgery, patients showed a continuing reduction in reward drive to eat measured by PFS at least a year after RYGB compared to before (292, 294). This is in line with the results discussed in Chapter 3, which suggested that the RYGB procedure reduces hedonic hunger and helps to facilitate long-term changes in eating behaviour. However, the current findings suggest that the increase in satiety gut hormones, particularly GOP, for one-month does not appear to impact reward drive to eat– unlike RYGB. One explanation for the absence of change in reward drive to eat with GOP is that the anatomical rerouting of the GI tract that we see following RYGB plays a role as well as the change in gut hormone levels. The brevity of the intervention period in the current study (one-month) compared with three months for the RYGB group may be an alternative explanation for this discrepancy. Moreover, reductions in hedonic hunger may be linked to weight loss following RYGB surgery (294). The percentage value of the weight loss achieved in the three months following RYGB surgery (18%) was significantly higher than the weight loss achieved after one-month on the GOP infusion (4%), even accounting for the difference in timescales. Lastly, the size of the current study may be underpowered in terms of detecting the effect of the infusion (n=16). Further research is needed to confirm this finding.

5.6.3. Eating behaviour following GOP infusion

In the current study, one-month of GOP infusion increased restraint eating significantly, as measured by DEBQ, in comparison to baseline figures. Similarly, three-month post-RYGB figures showed a significant increase in dietary restraint. The change from baseline between these two interventions in dietary restraint was similar and continued long-term after the interventions. RYGB was more effective than GOP in terms of reducing external eating at the three-month change from baseline in RYGB when compared to the one-month change post-GOP. Neither intervention impacted emotional eating at the same time-point. The main eating styles described in the DEBQ questionnaire relied on three theories that were used to explain

the process of overeating based on behavioural psychological factors such as stress, worry, anger or boredom rather than physiological signals of hunger. The psychosomatic theory refers to eating to cope with distress and relieve negative emotions such as depression, and disregards the physiological feelings of hunger (emotional eating) (584). In cases of negative psychological factors, normal-weight and underweight individuals tend to lose their appetite and eat less, while overweight individuals tend to respond by excessive eating, thus gaining weight. Secondly, externality theory suggests that the process of overeating can be triggered without internal feelings of hunger as a response to external cues such as the smell, sight or taste of food (Schachter, 1968) (external eating). Thirdly, the restrained eating theory is the opposite approach to the previous two theories, as it reflects an awareness of refraining from eating or restricting food intake to lose or maintain weight (restraint eating) (van Strien et al. 1986) (73).

The TFEQ was the second scale used in the current study to measure eating behaviour according to three subscales: Cognitive Restraint, Disinhibition and Susceptibility to Hunger. The TFEQ showed no significant change within the GOP group and no significant change from baseline between the GOP and the control group in any of the three subscales after one-month of infusion or two-month post-infusion. Figures for three months after RYGB surgery showed similar impacts in cognitive restraint and hunger according to the change from baseline compared with the change post-GOP infusion. However, RYGB showed greater effect in reducing disinhibition eating (loss of control) compared to post-GOP when the change from baseline was compared at three months and one-month respectively. The third scale used to measure eating behaviour was the EDE-Q, which contains four subscales: Restraint, Eating Concern, Shape Concern, and Weight Concern. The only change observed was in the RYGB group in terms of significantly reduced weight and shape concerns in comparison to the changes achieved after the GOP infusion. This is possibly due to the significant difference in

weight loss between the two interventions. In the following section, I will discuss the results of each eating style in comparison to the literature.

5.6.3.1. Dietary Restraint following GOP infusion

The findings in the current study on increased dietary restraint measured by DEBQ following both GOP hormones and RYGB, but not following the saline placebo are presumably mediated by the anorectic effects of gut hormones. No previous study has directly compared RYGB and GOP infusion in terms of restraint eating. The combination of higher restraint and feelings of satiety in weight loss efforts may increase the chances of successful outcomes. Although dietary restraint is commonly practised by overweight people and individuals with obesity in an attempt to lose weight or maintain weight-loss, previous studies showed a mixed impact of restraint on weight regulation. Some neuroimaging research on restraint eating suggests that restraint eating is related to the heightened responsiveness of regions of the brain that are associated with food reward, increasing the risk of binge eating and overeating. For example, Coletta et al. (2009) investigated the neural activity of normal-weight individuals using fMRI, and discovered that compared to unrestrained eaters (n=10), restrained eaters (n=9) show stronger activation to food cues in reward areas such as the orbitofrontal cortex in response to food pictures when fed. In addition, restrained eaters found palatable food more appealing and were less hungry when fasting (585). Demos et al.(2011) also reported that restrained dieters had higher reward responses in the nucleus accumbens – which is an important area in processing reward-related food – after a milkshake compared to water than unrestrained dieters (586). However, both Coletta's and Demos' study used the Restraint Scale to measure dietary restraint to identify individuals who expend significant effort towards dieting, rather than those who are successful at limiting their food intake and/or losing weight. This is often followed by disinhibited eating in some settings (587), so this type of restraint was found to be associated with unsuccessful long-term weight loss. In a review of the literature on personality and dietary

restraint as measured by commonly-used self-reporting assessment instruments, Mills et al. (2018) concluded that different measures of restraint capture different personality profiles with different eating behaviour (434). Caution should therefore be exercised when interpreting the results of dietary restraint. DEBQ-restraint can be subdivided into the intentions to restrict food intake that accompany weight-loss attempts and the actual behavioural restraint that use more flexible strategies to control energy intake and are thought to represent more successful dieters (432). The type of restraint was discussed in the current findings as being identified by the DEBQ (69, 70), which is associated less with emotional and externally induced eating and includes successful rather than unsuccessful attempts at food restriction (433). The DEBQ is a robust instrument that can be used to identify several eating styles (581) and includes questions such as *'Do you take into account your weight when deciding what you eat?'*. Neumann et al. (2018) studied the trajectories of eating behaviour in individuals with successful weight-loss maintenance using the DEBQ (n=440). They showed that dietary restraint measured according to the DEBQ seems to be necessary for successful weight-loss maintenance over two years (270) and is associated less with emotional and externally induced eating (433).

The TFEQ is another commonly used tool that is used to assess eating behaviour traits by measuring restraint, disinhibition and hunger. Interestingly, there were no differences in restraint eating measured by TFEQ between or within groups in the current study, emphasising the idea that different measures of restraint capture different personality profiles with different eating behaviour. Restraint has been shown to be influenced by bariatric surgery and impact on weight loss success (74, 256). Adapting to a dietary change after weight loss surgery is influenced by individual psychological eating behaviour traits that could disturb or favour weight loss success (256). Comparative RYGB studies are not always consistent in terms of the impact of surgery on restraint eating. Laurenius et al. (2012)(221), Petereit et al. (2014)(454), Konttinen et al. (2015)(588) and Hubert et al. (2019) (221, 276, 450, 454, 589)

used the TFEQ, while Karlsson et al. (2015) used the DEBQ, reporting an increase in dietary restraint, while Bryant et al. (2013) and Søvik et al. (2013) using the TFEQ and Pepino et al. (2014) using the DEBQ (268, 452, 590) reported no change. The inconsistency of findings could be explained by several sources of variability including differences in measures used to capture behaviour, time since surgery, percentage of weight loss and the other personality traits, and these factors combined may affect the result.

Overall, restrained eaters, as identified by the DEBQ, use more flexible and therefore more successful strategies for dieting which can actually promote weight control (591), rather than rigid or inflexible strategies that are often seen in "yo-yo" dieters, for whom weight fluctuations are common.

5.6.3.2. Emotional and external eating following the infusion

Interestingly, one-month of GOP infusion did not alter emotional or external eating at any time-point, suggesting that anorexigenic gut hormone infusions do not impact emotional or external eating. Similar findings were observed at three-month post-RYGB which contrasts with the findings in the literature, suggesting that despite the loss of reward values from food seen in PFS in the current study, RYGB patients may continue to use food for emotional regulation. In contrast to the findings of the current study, Pepino et al.(2014), using the DEBQ, showed a significant reduction in emotional eating soon after surgery (269) and maintenance of this reduction for up to a year post-surgery (221). Although the latter study used the 21-item TFEQ that measures emotional eating, cognitive restraint, and uncontrolled eating rather than the DEBQ, which may explain the difference in results. In terms of external eating, there were significant changes from baseline between one-month of GOP and three months post-RYGB as measured by the DEBQ. Postoperatively, patients showed a significant reduction in external eating for up to one-year post-surgery (see Chapter 3). The reduction in the effect of external stimuli – such as the sight or smell of food post-RYGB – could be due to the reduction in

reward drive to eat that was observed post-surgery but not post-GOP in the current study – again measured using the DEBQ. No study has examined those variables following the infusion of gut hormones. We can therefore conclude that the level of satiety gut hormone – which increases after surgery – may not be the main reason behind the changes we observed in these behaviours.

In terms of shape and weight concerns, the findings in the current study showed a significant reduction in shape and weight concern at three-month post-RYGB when compared to baseline and after one-month of GOP. These findings may be explained by the greater weight loss following RYGB compared to GOP. After RYGB and after weight-loss, patients experience a reduction in weight and shape concerns (223). In the current study, the RYGB group may have simply experienced a greater degree of satisfaction with the degree of improvement in their body weight compared to GOP patients. However, another explanation may relate to unresolved emotional conflicts regarding overeating, and therefore weight, in GOP patients who did not experience a reduction in reward drive to eat in the current study compared to the RYGB patients, who did.

5.6.3.3. Disinhibition (uncontrolled eating) following the infusion

Disinhibition eating after the GOP infusion was measured using the TFEQ. Unlike the post-RYGB group (Chapter 4), which showed a significant reduction in disinhibition eating for up to a year post-surgery, a month of GOP infusion had no noticeable effect on disinhibition eating patterns at any point. The reduction in disinhibition that was observed after RYGB in the current findings is a favourable change that may support long-term weight loss success. In a case-control observational study that was aimed at comparing eating behaviour in women living with obesity preoperatively and one-year after bariatric surgery, Hubert et al. (2019) found that post-surgical patients had greater restraint and less hunger and disinhibition than they had pre-operatively (276). This finding was not observed post GOP infusion, suggesting

that the reason behind the reduction in post-RYGB disinhibition behaviour is not related to a post-surgery rise in postprandial anorexigenic GOP hormones. Another explanation might be that the duration of the GOP infusion was not of sufficient duration to mimic the results observed three-month after RYGB surgery. This means that the difference in assessment timescales (one-month post-GOP versus three months post-RYGB) might help explain the results. It should be noted that in the current study, the score for disinhibition eating post-surgery was the same as the GOP score, which did not change post-infusion.

5.6.4. Psychological status following the infusion

In addition to eating behaviour, psychological traits such as impulsivity, depression and anxiety are found to be related to obesity and overeating.

5.6.4.1. Impulsivity, depression, and anxiety following the infusion

The current findings showed no significant changes post GOP infusion in the impulsivity or in the reward sensitivity (reward responsiveness, reward drive, hedonic or behavioural inhibition), or in levels of depression and anxiety as measured by the Barratt Impulsiveness Scale, the Behavioural Activation, and Inhibition Scale (BAS /BIS), or the Beck Depression Inventory-II and the Hospital Anxiety and Depression Scale (HADS) respectively.

5.6.5. Weight-related quality of life following the infusion

Improvements in quality of life have always been reported after weight loss, regardless of the method of the weight loss (277, 499). GOP infusions did not show any significant changes post infusion compared to the saline infusion group, although there was a significant reduction in weight loss post-GOP. In Chapter 3 of the current study, RYGB surgery is seen to lead to significant improvements in health-related quality of life in general, which may be because the surgical group started with a poorer quality of life or achieved lower weight loss compared to the GOP group.

5.6.6. Food intake following the infusion

The current results show that a one-month infusion of GOP led to a significant reduction in food intake, representing a 36% and 20% reduction in food intake for the GOP and control group respectively. The reduction in food intake observed in the GOP group (-753.6kcal/day) did not change significantly when compared to the reduction reported three months after RYGB surgery (-945.6 kcal/day) (change from baseline). We chose to investigate food intake three months post-RYGB compared to one-month after GOP in a dose that replicated the level of GOP post-RYGB, as by this time patients who had undergone operations at the IWC were expected to tolerate solid food and start eating normally. The reduction in food intake post anorectic gut hormone infusion is in keeping with other studies that show a reduction in food intake of around 27% (574) and 30% (577) following a combined infusion of PYY and GLP-1 infusion, and of around 42% using a combination of PYY and OXM (578). However, other studies (574, 577, 578) differed from the current study in several ways. The first of these is the assessment criteria for food intake (food-dairy in the current study versus buffet meals and *ad libitum* intake); the second is the duration of the infusion (chronic versus acute infusions), while the third covers the method of administration of the hormones (**SC** versus **IV**), and the fourth was the nature of the population used (only participants with obesity versus a mixture of participants with obesity and normal-weight and overweight patients). All the previously mentioned studies reported higher anorectic effects based on a combination of GLP-1 and PYY (574, 577) and PYY and OXM (578) compared with infusions of either of these hormones on their own. The reduction in calorie intake observed for chronic GOP patients in the current study – a 36% reduction measured using a 4-day food diary compared to a 42% reduction measured using *ad libitum* approaches (1) – replicates the reduction in total calorie intake observed during the acute infusion of GOP during the Dose-Finding Study (a 32% reduction) measured by *ad libitum* energy intake (197). This appears to suggest that the anorectic effect

of GOP infusions can be sustained over time with no loss of potency. Studies over a longer period suggest a more sustained reduction in EI of about 30% (2 years) and 20% (10 years) post-operatively (221, 580).

It has been proposed that overall reduction in food intake might be one of the mechanisms associated with weight loss after obesity surgery, although evidence relating to changes in the macronutrient content of meals is inconsistent (228, 592, 593). In the current study, the macronutrient distribution of total caloric intake per day post-GOP did not change significantly when compared with pre-GOP levels or the saline infusion control group. However, the impact of GOP on the percentage of carbohydrates and fat consumed was significantly different to the impact of the RYGB. GOP participants consumed about 4% less carbohydrates and 3% more fat compared to before infusion, while the RYGB participants consumed about 1.3% more carbohydrate and 6% less fat compared to before surgery. In the longest prospective study, which involved 80 patients, the reduction in fat intake was still measurable 8 years after RYGB surgery compared to before (228). The same study reported an increase in the percentage intake of protein, but no change in carbohydrate intake. In general, lower fat intakes were observed post-RYGB (182, 224, 225).

To the best of my knowledge, no study has investigated the impact of gut hormone infusions on the consumption of macronutrients. Further studies on the impact of surgery and the surge in gut hormones post-surgery on the macronutrient content of a meal are required.

5.7. Conclusion of GOP infusion study

The surge of the three anorectic gut hormones after RYGB (GOP) may not contribute to positive changes in eating behaviour, hedonic drive to eat or health-related quality of life when compared to those observed following RYGB surgery. However, anatomical changes that occur after surgery that are linked to alterations in combined neural and hormonal signals may explain the favourable behavioural changes that are reported after RYGB. Such changes may also result from the surgical re-routing of the GI tract rather than the infusion of gut hormones with no associated anatomical alterations.

5.8. Limitations

The preliminary results seen in this study have some limitations. The sample size for the infusion study was comparatively small and the study maybe was not powerful enough to detect significant differences in eating behaviour implying a high risk of type-I statistical error. Another potential limitation is related to the possibility of selection bias, which can decrease the representativeness of the study samples. Although both the infusion group and the surgical group followed the same eligibility criteria, the infusion group's participants were selected via advertisements and the RYGB participants were selected from the waiting list for bariatric surgery. I tried to avoid samples that do not reflect my target population by picking those who belong to certain groups. The GOP infusion lasted for one-month, and the study was designed using a single-blind approach – mainly for participants' safety, because a combined infusion of three anorectic hormones has not been tried before. However, future studies are being prepared to incorporate a double-blind design and to increase the timescale of the infusion. Further study is warranted to overcome the current study limitations and to determine whether anorexigenic gut hormones are involved in the change in eating behaviour or reward drive to eat seeing after RYGB.

6. CHAPTER SIX:

INFUSION STUDY (PART 2)

The Effect of a Chronic Infusion of GOP on the Sensitivity, Intensity and Reward Value of Sweetness in People with Obesity and Type 2 Diabetes

Part 1 of the Infusion Study (Chapter 5) showed that a one-month subcutaneous infusion of GLP-1, OXM and PYY (referred to as 'GOP' respectively) gut hormones to mimic peak postprandial RYGB circulating levels in participants living with obesity and T2DM did not produce the same favourable changes in eating behaviour that were reported after RYGB. The current chapter explores whether alterations in taste preferences following bypass surgery may be caused by changes in circulating gut hormones which in turn may contribute to the success of the operation.

6.1. Introduction

Obesity is associated with eating habits that are characterised by stronger preferences for energy-dense foods such as fatty and sugary foods (594-597), increasing the consumption of this kind of foods (598-600). These unbalanced eating habits could also be explained by a reduction in taste sensitivity, as well as blunted brain reward activation in response to palatable food, which has been observed in overweight and obese individuals (395, 601-604). Patients who underwent bariatric surgery report changes in taste, appetite, and food preferences as well as a reduction in interest for sweet and high-fat food (230, 243, 248, 269, 396, 397, 410, 605-607). Surgery-related changes in taste perception have been considered as mechanisms that contribute to a move towards healthier food preferences after RYGB surgery. Taste can be divided into three domains: sensory, reward, and physiological (245). Changes in the sensory taste domain deal with the ability to detect different stimuli and may accordingly impact food cravings and food selection. The recognition and detection thresholds for taste perception have been investigated using sensory discrimination methods such as taste strips (608), or sucrose detection thresholds (232). In 1994, Scruggs et al. were the first to investigate the impact of RYGB on taste acuity among women with obesity, and their study reported a trend towards a reduction in the sensory domain of taste (sweet detection and recognition threshold). Following these findings, Burge et al. (1995) were the first to show that RYGB may affect the sensory

domain of sweetness (243). A series of more comprehensive experiments were subsequently conducted, which reported changes in taste sensitivity with improved sweet detection postoperatively, resulting in a more intense perception of sweetness (232, 243, 608-610). This change in taste perception may drive a change in food choice, which may explain Halmi et al's findings of a significant reduction not only in the amount of food eaten using the 24-hour dietary recall method, but also in the consumption of high calorie, high-carbohydrate and fatty foods 6 months after RYGB surgery and throughout the 24-month study period (182).

Other studies have reported a reduction in the consumption of sweets or desserts for up to two years following RYGB using indirect methods such as verbal reports, 24-hour dietary recall, and a variety of dietary surveys (224, 226, 230, 292, 611). Moreover, candidates for bariatric surgery appeared to crave foods more frequently than individuals of normal body weight before they had surgery (612). A reduction in such cravings – particularly for sweet foods – was observed after RYGB in adults (261, 268, 269, 612) and adolescents (613, 614), measured using the Food Craving Inventory. Interestingly, a reduction in the frequency of food cravings was also observed following weight loss using behavioural weight loss programmes (269, 536, 538, 614). This suggests that food cravings have a significant effect on weight loss and that weight loss itself may drive changes in cravings. A loss of control over body weight is associated with frequent food craving (615), while higher levels of weight loss can be associated with fewer incidences of craving (616).

The reward taste domain can be divided into consumption and appetitive components (liking and wanting respectively) (246). Ochner et al. (2012) in their study of people undergoing RYGB, discovered that the activation of the reward areas towards high-calorie food cues following RYGB surgery was reduced (410). Functional MRI studies (223, 386) have shown a greater degree of change in the activation of the reward areas (including the ventral tegmental area, the orbitofrontal cortex, amygdala, caudate nucleus, nucleus accumbens and

hippocampus) to different food tastes and visual food stimuli post-RYGB compared to pre-operatively (386) and compared to gastric band operation (223). In a more recent study, Smith et al. (2020) were the first to directly measure changes in taste preferences and taste-induced brain responses among RYGB patients in comparison to VSG patients. Both surgical procedures resulted in a decreased liking of sucrose-sweetened foods, but RYGB patients who achieved greater weight losses showed greater changes in taste-induced BOLD signals in the ventral tegmental area (VTA) within two weeks of surgery, a result that was not mirrored in VSG patients (386). In their cross-sectional study, Scholtz et al. (2014) observed a reduction in the activation of reward responses to high-calorie food pictures over low-calorie foods in RYGB patients when compared to the gastric banding group. Using Visual Analogue Scales (VAS), the RYGB patients considered pictures of high-calorie foods to be less appealing and found that sweet foods that are high in fat, such as ice cream, were "less pleasant to eat" in comparison to patients who had gastric bands fitted (223).

The exact mechanism governing the reported changes in taste acuity and reward responses that were observed post-RYGB is complex and not yet fully understood. The postprandial elevation in anorexigenic gut hormones such as GLP-1 are possibly related to observations in this study of a reduction in taste thresholds for sucrose after RYGB surgery. GLP-1 receptors are usually expressed on taste afferent nerve fibres, and mice whose GLP-1 receptors have been removed are reportedly less responsive to lower concentrations of sucrose using a brief-access licking test (617, 618). This indicates that sufficiently high GLP-1 plasma levels might affect peripheral taste signals. In the small bowel, enteroendocrine cells sense the presence of carbohydrates in ingested nutrients, releasing anorexigenic GLP-1 and PYY hormones (619). The administration of GLP-1 and PYY to rodents resulted in conditioned taste aversion through the activation of brain-stem neurons (620, 621). The expression of T1R2 and T1R3 taste receptors, which respond to sweeteners and gut hormones, has also been shown to be altered

after RYGB, but a causal relationship between this and changes in taste or food preferences after RYGB has not been proved (232). Recently, Kadouh et al. (2020) conducted a double-blind, placebo-controlled, randomized 16-week trial to investigate the effects of Liraglutide treatment (a GLP-1 analogue) compared to placebo on taste preferences in individuals with obesity using VAS every 30 minutes over 5 hours after ingestion of a standard liquid breakfast. They found that Liraglutide reduces the desire to eat sweet foods when compared with the placebo (385). Studies examining the effect of OXM on taste function are rare. As far as PYY is concerned, the peripheral administration of $PYY_{3–36}$ has been reported to cause conditioned taste aversion in mice (621), while a chronic increase in salivary PYY_{3-36} synthesised in the taste buds of the mice's tongues can reduce food intake (622). Following the previous chapter, which examined the impact on eating behaviour of a chronic infusion of anorexigenic gut hormones, this chapter considers anorexigenic gut hormones as mediators of the change in taste functions.

6.2. Research aim

This research aims to investigate:

1- The effects of an exogenous gut hormone infusion (GOP) on sweet taste detection thresholds (sweet sensitivity) among patients with obesity and with type 2 diabetes mellitus using the constant stimuli method.

2- The effects of GOP on sweet taste intensity and consummatory reward value using visual analogue scales.

6.3. Research hypotheses

The reproduction of an elevation in gut hormones using an infusion will lead to:

1- A reduction in the sweet taste detection threshold.

2- An increase in the sweet taste intensity ratings reduces the consummatory reward value of sweet taste.

6.4. Methodology

This study was designed as a prospective interventional study to measure changes in taste perception among individuals with obesity and T2DM. Participants (N=34) were randomised into the GOP arm (16) who received the hormone infusion, and the control (saline placebo) arm (12). Testing was carried out at baseline and after one-month on the infusion using the methodology described by Bueter et al. (2011) (232). For the full details of the study methodology see Chapter 2.

1- **Sweet (sucrose) taste sensitivity detection threshold** using the constant stimuli method of sucrose detection sensitivity. After fasting overnight, infusion participants were asked to evaluate seven different sucrose concentrations to determine sweet detection thresholds pre-and post-infusion. Participants were asked to hold the solution in the mouth for 5 seconds and swirl it around before spitting it into an empty container without swallowing. They were then asked whether the solution contained sugar or just water. For the full details about the study methodology (see Chapter 2 section 2.4.5.1).

2- **Intensity of sweetness test** using the "sip and spit" technique. This test was carried out immediately after the sweet taste detection test. Participants were asked to evaluate five ascending sucrose concentrations. All solutions were stored at 4˚C and presented cold for testing. Participants were asked to hold the solution in the mouth and rate the solution intensity using the Intensity Generalised Labelled Magnitude Scale (gLMS). For more details about the test and the gLMS (see Chapter 2 section 2.4.5.2).

3- Sweet taste consummatory reward (liking). This test was also carried out using the sip and spit technique and the same solutions. However, the consummatory sensory and reward value of taste lends itself to the use of two visual analogue scales (the Just

About Right [JAR] scale and the reward [Liking] gLMS scale). For more details about the JAR and gLMS scales see Chapter 2 section 2.4.5).

6.4.1. Statistics

6.4.1.1. *Data analysis*

6.4.1.1.1. Data analysis for sucrose taste detection sensitivity

The full description of the data analysis process was presented in Chapter 2 section 8.2. The hit rate for each sucrose concentration was adjusted to account for false alarms to produce a corrected hit rate using the following equation:

$$Corrected\ hit\ rate = \frac{P(hit)-P(FA)}{1.0-P(FA)} \quad (232)$$

Where *P (hit)* represents the proportion of solutions of a given concentration that were correctly identified, and *P (FA)* represents the proportion of solutions that were false alarms. Concentration response curves were produced to represent the corrected hit rate values for each participant for each test (at baseline and one-month on the infusion) to provide a group of individual psychometric functions through using the following equation:

$$F\ (x) = \frac{a}{1+10^{((log10(x)-C)*b)}} \quad (232)$$

Where $log^{10(x)}$ represents the $\log^{10}$ concentration, *a* represents the upper asymptote of performance (the maximum is 1), *b* represents slope, and *c* represents the log10 concentration at ½ a performance (EC50, which is defined as half-maximal effective concentration). The c parameter was defined as the threshold value, as it represented the inflexion point of the psychometric function, thus optimally representing horizontal shifts in sensitivity. The experiment only compared the c-values of participants' curves where the fits accounted for at least 85% of the variance. These c-values were calculated using Mystat® (Systat® 12)

software. The movements in *c* parameters were analysed using the mixed-effects model in IBM SPSS 24.

Participants ratings on the scales (Intensity generalised labelled magnitude scales, Just About Right visual analogue scales, liking generalised labelled magnitude scales) were measured with a ruler, and the mean ratings for each concentration of the solution were measured and analysed.

6.4.1.2. *Statistical analysis:*

Normality was assessed using Shapiro-Wilk normality test. The dependent variables used for 2-way repeated measure **ANOVA** analysis were created by averaging each set of ratings across the trials for each of the seven concentrations (the corrected hit rate values for the taste detection thresholds). The ratings on the VAS scales were also analysed using 2-way **ANOVA**. For baseline comparison between groups, an unpaired t-test was applied. A p-value of 0.05 was considered statistically significant. The data analysis was conducted using Graph Pad Prism version 9 (GraphPad Software, San Diego, USA) unless stated otherwise.

6.5. Results

Of the 34 participants recruited for the food preference sub-study of the infusion trial, 28 completed the study (16 from the GOP arm, and 12 from the control arm). Six participants did not complete the study for different reasons (see Chapter 2, Figure 5 on Page 86). There were no significant differences between the groups in terms of age, weight, BMI, and gender distribution (see Table 28 on Page 238).

6.5.1. Sweet taste detection threshold

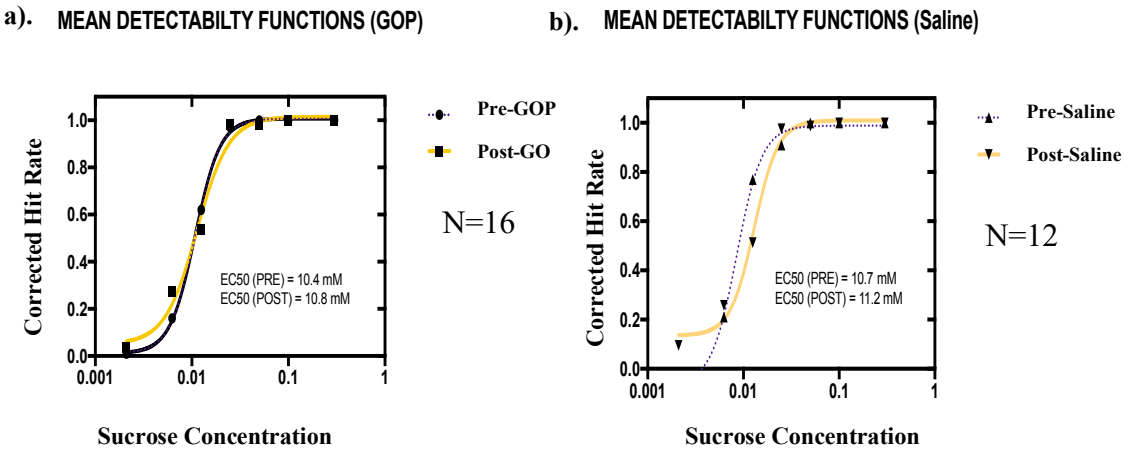
The sweet taste detection threshold was measured using the method of constant stimuli (Sensory domain). There was no significant change in sweet taste detection thresholds between GOP and saline groups at baseline using an unpaired t-test (P= 0.35). There was also no significant change in the sweet taste detection threshold either within (pre compared with post-infusion using 2-way **ANOVA** (corrected hit rate, P= 0.28; EC50, P= 0.62) or between groups (post-GOP compared with post saline infusion (corrected hit rate, P=0.96; EC50, P=0.21). See Figure 10 on Page 239.

Table 28: *Baseline characteristics of the studied participants (GOP/Saline)*

	GOP N=16	**Saline N=12**
Gender (F:M)	(7:9)	(6:6)
Age (years)	54.8±2.4	52.3±2.7
Weight (kg)	111.5±6.5	119.1±6.9
BMI (kg/m^2)	38.5±1.6	39.5±1.5
T2DM, n (%)	13 (81.25)	8 (66.6)
Prediabetic, n (%)	3 (18.75)	4 (33.3)

Data are presented as mean±SEM for GOP and saline at baseline. One-way ANOVA tests were applied for comparison between groups, and a Fisher exact test was used for categorical data. Prediabetic includes impaired glucose tolerance, impaired fasting glucose, or HbA1c of 6.0–6.4% (42–48 mmol/mol). Abbreviations: BMI, Body mass index; T2DM, Type 2 diabetes mellitus.

Figure 10: *Corrected Hit Rates from the Sweet Taste Detection Threshold Tests*



a). Curves of the mean corrected hit rate for 16 participants over time for GOP (left) and saline (right) as a function of sucrose concentration. The EC50 was derived from the c-parameter in the curve fit and represented the concentration at which the corrected hit rate reaches 50% of the maximum asymptote. There was no significant difference in the EC50 within groups (pre-GOP vs post-GOP, P=0.62; pre-saline vs post-saline, P= 0.30) or between groups (post-GOP vs post-saline, P=0.21) using 2-way ANOVA.

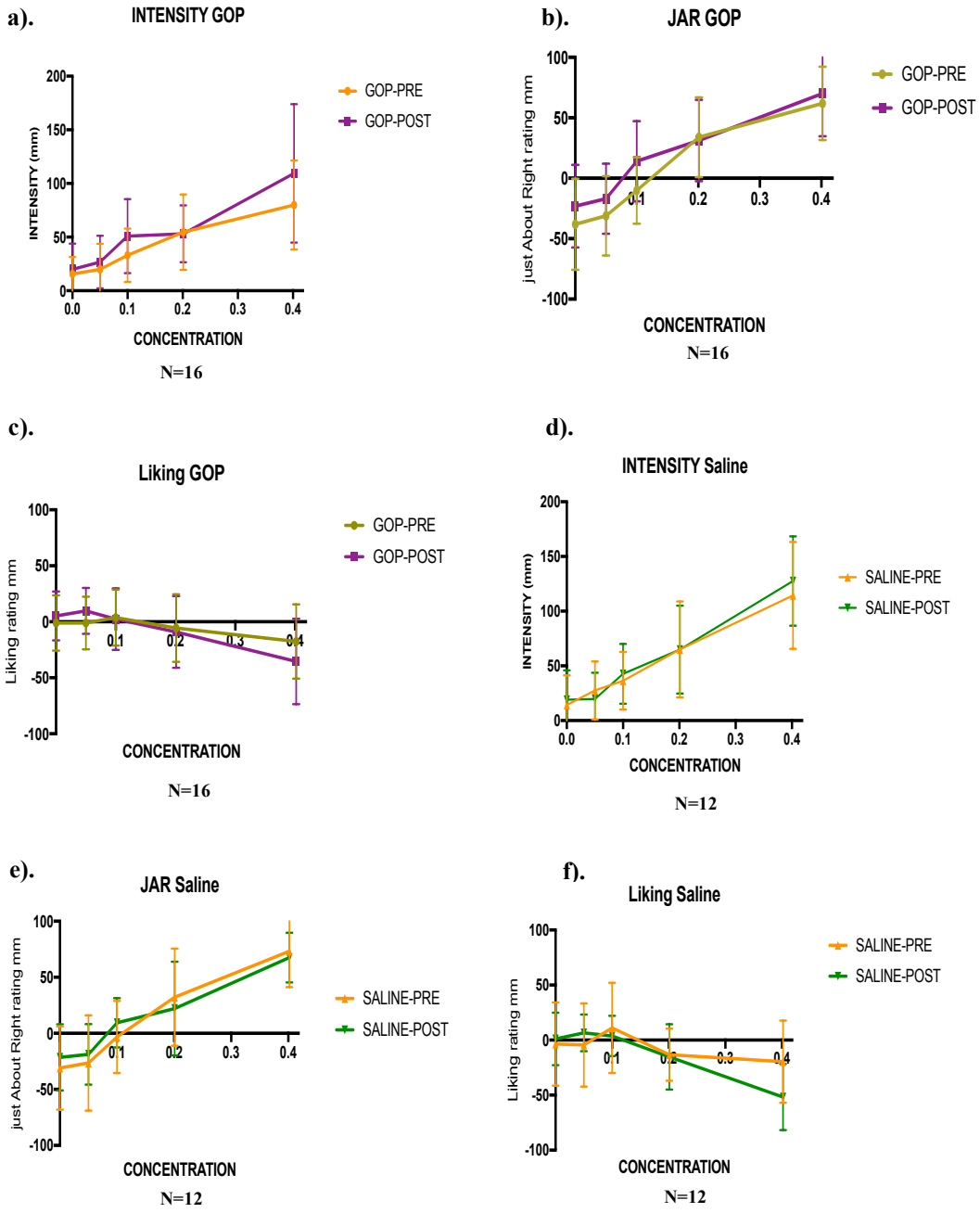
6.5.2. Sweet taste intensity

Sweet taste intensity was measured using the general Labelled Magnitude Scale (gLMS). There were no significant changes in sweet taste intensity between GOP and saline at baseline using an unpaired t-test (P=0.62). There was no significant change in intensity either within-group (pre-GOP vs post-GOP P=0.11; pre-saline vs post-saline P=0.40) or between-group comparison (post-GOP vs post-saline P= 0.91) using 2-way **ANOVA** (Figure 11 on Page 241).

6.5.3. Consummatory reward value of sweet taste

Consummatory reward value of sweet taste was measured using the Just About Right (JAR) and pleasantness VASs. There was no significant change in the consummatory reward value of sweet taste either within or between groups at any of the time points using JAR scale and liking scale using 2-way **ANOVA** (Figure 11 on Page 241).

Figure 11: *Intensity and consummatory reward value of sweet taste assessed by gLMS, VAS, and JAR*



The two curves of the mean corrected hit rate for 16 showed: a). No significant differences in sweet intensity pre-GOP compared with post-GOP; b). No significant differences in JAR scale pre-GOP compared with post-GOP; c). No significant differences in liking scale pre-GOP compared with post-GOP. The two curves of the mean corrected hit rate for 12 participants showed: d). No significant differences in sweet intensity pre-saline compared with post-saline; e). No significant differences in JAR scale pre-saline compared with post-saline; f). No significant differences in liking scale pre-saline compared with post-saline. The comparison was performed using 2-way ANOVA.

6.6. Discussion

6.6.1. Summary of GOP findings

This chapter investigates one of the potential mechanisms to explain the alteration in sweet intake, i.e., the surge in gut hormone levels that is associated with RYGB operations, and which may modulate gustatory function. We tested the hypothesis that an infusion of GOP affects the consumption of high-calorie sweet foods, partly by changing patients' sweet taste function. To investigate this hypothesis, a single-blind randomised controlled trial was conducted to compare the exogenous infusion of triple anorexigenic gut hormones (GOP) with saline in individuals with obesity and T2DM. The findings showed that a subcutaneous GOP infusion over one-month, with target doses that mimicked the postprandial post-RYGB GOP level (doses of 4, 4, and 0.4 pmol/kg/min of GLP-1, OXM, PYY respectively) for 10-12 hours a day did not alter the participants taste functions. The taste functions tested included sensory-discriminative components (taste detection thresholds and intensity) and reward components (JAR scores and gLMS ratings for sucrose). These were determined using constant stimuli and the "sip and spit" technique, echoing the work of Bueter et al. (2011) (232).

6.6.1 Sensory-discriminative component of taste perception

6.6.1.1 Sweet taste detection threshold using constant stimuli

The study showed no change in sweet detection thresholds after GOP infusion, suggesting that the exogenous increase in gut hormones without the anatomical alteration achieved by RYGB does not lead to any change in taste sensitivity in terms of sucrose detection and recognition thresholds. Little is known about the effect of gut hormones on taste perception in humans, but in animal studies, Shin et al. (2008) showed that GLP-1 receptor knockout mice experienced a reduction in sweet taste sensitivity, suggesting that GLP-1 enhances sensitivity to sweet tastes (618). In mice, a chronic increase in salivary PYY_{3-36} synthesised in the taste buds of the tongue

resulted in a significant long-term reduction in food intake and body weight (622). The peripheral administration of PYY_{3-36} can also cause a conditioned taste aversion in mice through the activation of brainstem neurons (621). The inhibition of food intake by $PYY_{3–36}$ may therefore result in part from the induction of an aversive response. No previous trials exist that assess the direct impact of a triple gut hormone infusion (GOP) on taste functions. However previously published literature on RYGB and taste function exists, and we may understand our findings more in this context.

When compared with surgical studies, the current findings are consistent with Nance et al. (2018), who reported no changes in taste detection or recognition thresholds after bariatric surgery (27 RYGB, 8 SG; compared with one-year postoperatively) as determined by a two-alternative forced-choice staircase method (261). Using the same method, Pepino et al. (2014) also found no changes in sweet detection thresholds in women who had undergone bariatric surgery (17 RYGB, 10 BAND) measured at baseline and after a 20% weight loss (269). Problems associated with these studies include the absence of a control group and the expectation bias associated with the staircase method. The staircase approach involves repeatedly presenting a variable stimulus and is adjusted upwards when it is not perceived and downwards when it is perceived, and for difference thresholds a variable stimulus is adjusted to increase its absolute difference from a standard stimulus whenever the difference is not detected or is adjusted to decrease its absolute difference from the standard stimulus whenever the difference is detected. The expectation bias associated with the staircase method was overcome in the current study by using the repeated stimuli method. Seven different concentrations of sweet solution, each sweeter than the last, were offered eight times to participants who were chosen in random order, making 56 trials in all. The solutions were randomly interspersed with water (also 56 times) giving the participants no prior knowledge or expectations of what the next stimulus would be. However, the result of this study – that sweet

taste detection thresholds remain unchanged – is not consistent with Bueter et al's (2011) study, which used the same methodology and found a significant reduction in EC50 concentrations. In their study, sweet taste detection decreased while taste sensitivity increased for individuals with obesity over the two-month period following RYGB surgery, a result that suggests that their ability to detect sweet taste was improved (232). Meanwhile, a prospective trial run by Burge et al. (1995) studied changes in taste acuity for 14 individuals (8 women, 6 men) after RYGB and compared the results with 4 individuals consuming a VLCD. They used the staircase method before and 6 and 12 weeks after the start of the intervention, concluding that all RYGB patients reported changes in taste perception and modified their food choices to reflect the fact that food tasted sweeter. These results were not reflected in the VLCD group, although sample sizes were small. RYGB patients reported greater sensitivity to sweet foods, leading to a decreased consumption of high-calorie comfort foods, helping surgery-related weight loss and weight loss maintenance (243). There is strong evidence of profound differences between men and women in terms of sense of taste, but the underlying mechanisms need to be investigated further (623, 624). Sex hormones are likely to play a substantial role (625).

6.6.1.2 Sweet taste intensity using the general labelled magnitude scale (gLMS)

The current study found that the GOP infusion had no significant impact on sweet taste acuity compared to the control group. This lack of change is consistent with Nance et al. (2018), who measured intensity post-RYGB using the gLMS approach (261). However, Pepino et al. (2014), who also used the regular gLMS to measure intensity, reported a small reduction (-7±5%) in the perceived taste intensity of sucrose two-month after RYGB (269). So far, no studies have investigated the effects of a gut hormone infusion on sweet intensity detection. The discrepancy from the RYGB findings may be due to variations in the methodologies used,

including differences in time since surgery (one-year vs 20% weight loss), postsurgical weight loss and gender distribution (both genders vs only females).

6.6.2 Reward component of taste perception

6.6.2.1 Consummatory reward

The reward domain of taste encompasses the concept of consummatory reward ("how much do you like this food?") and appetitive reward ("how hard are you willing to work for it?") (246). Although we examined changes in consummatory reward after hormone infusion in comparison to a control group, measuring changes in appetitive reward was beyond the scope of this study due to limitations in manpower and resources. The current study investigated changes in the consummatory reward value of sweet taste in individuals living with obesity and T2DM, which showed no significant change using either the JAR or the gLMS reward scale following chronic gut hormone (GOP) infusion when compared to the control group. Results from studies that investigated the consummatory responses (number of licks) of rodents after RYGB using the brief access test with a series of sucrose concentrations were also contradictory. Mathes et al. (2012) investigated the effects of injecting post-RYGB and a control group of rats with GLP-1 agonists (exendin-4) or antagonists (exendin-9) on sucrose licking using the brief-access test to assess consummatory behaviour. They reported that neither the alteration in GLP-1 levels nor in GLP-1-receptor activity changed consummatory responsiveness to sucrose (626), which is consistent with the findings in this study where post-GOP infusion did not result in changes in consummatory responsiveness to sucrose. However, Shin et al. (2008) reported a dramatic reduction in taste responses to high concentrations of sucrose post-RYGB in GLP-1-receptor knockout mice (618). Shin's finding is consistent with Tichansky et al. (2011) (627) and Hajnal. et al. (2010) (426), who demonstrated that rats after RYGB had lower preferences for sweet taste. Similarly, in human studies, Pepino et al. (2014)

used the sweet palatability test, asking participants to rate different concentrations of sucrose using the gLMS. This method is considered superior to standard VAS tests for measuring taste. Pepino's study concluded that patients experienced a shift in the palatability of sweet tastes after RYGB, but not after gastric band surgery. In contrast to previous findings but in line with this study, Bueter et al. (2011) found that when using the 'just about right' VAS, there was no effect on reward taste ratings of sucrose for RYGB patients (232). These varying results in animal studies and between human studies may be due to different methodologies, different animal species used, different levels of weight loss and differences in timing measurements after surgery between research groups. We can therefore draw no definitive conclusions from these results on the effect of GOP or RYGB on taste ratings.

Nance et al. (2020) recently reviewed the literature on changes in taste function following bariatric surgery (RYGB and SG) to examine the differences in findings according to the methodologies used (indirect vs direct measurements) (628). They concluded that the use of indirect data (self-reported questionnaires to determine changes in sweet taste) showed distinct changes in taste that can be linked to the decreased consumption of sweet foods after bariatric surgery. However, these self-reported taste changes were not apparent when using validated sensory methods and real-life studies under supervised conditions. Considered in this light, the studies suggest that changes in taste perceived by patients after bariatric surgery lie beyond the function of peripheral taste (i.e., taste buds) and can be associated more with changes in the brain that relate to the reward and reward value of food, which can also affect consumption and the recall of consumption. Chapter 3 of this thesis found support for the premise that RYGB surgery alters the reward value of food, as this study reported a long-term reduction in food reward responses after surgery using the PFS. Further behavioural evidence on the effects of GOP on taste function could be obtained by looking at consummatory paradigms in patients, in which they are not asked to rate their perception of taste but by using objective measures

such as filming facial expressions to establish participants' unspoken responses when food is ingested.

Collectively, the current findings suggest that the surge in satiety gut hormones, particularly GOP for one-month, does not appear to explain altered taste functions. An alternative explanation may be that the anatomical rerouting of the GI tract that we see following RYGB plays a role by altering the positions and the anatomical construction of the gut. An alternative explanation for why we did not see the change in taste with GOP is that the duration of exposure to the GOP infusion in this study design was not sufficient to have a statistically significant impact on taste function. Furthermore, unlike Bueter et al. (2011) (232) who reported an improvement in sweet detection in non-diabetic patients two-month postoperatively, the group of the current study included diabetic patients. There is some evidence that taste molecule expression is lower in diabetic patients (629), which may have impacted the current results. Moreover, the satiety hormone leptin may also influence sensitivity to sweet taste, and levels of this hormone are found to diminish after weight loss. Kawai et al. (2000), showed that Leptin suppressed the sweet-sensing receptors in studies on animals. These studies showed a reduced response of taste nerves to sucrose after injections of leptin, an effect that was not apparent in mice with no Leptin receptors (630). Umabiki et al. (2010) concluded that changes in leptin serum levels may correlate with changes in sweet taste thresholds. Umabiki's study found that leptin levels decreased significantly during a weight-loss programme for women with obesity, which may be associated with an overall lowering of sweet taste thresholds (631). However, in this trial, leptin levels were not measured. We may expect that reduced Leptin concentrations would increase sweet taste sensitivity alongside weight and mass loss, but the current study did not examine this. Alterations in taste function are likely multifactorial, including weight loss factors. Some researchers have shown increases in sweet taste detection thresholds after weight loss in general (632). Although GOP participants achieved a 4% weight loss after one-month

on the infusion, weight loss induced by RYGB (--%) may have greater effects on taste perception compared to weight loss induced by GOP, suggesting that post-operative changes can be enhanced by weight loss. In keeping with the potential effect of weight loss *per se*, Yoshino et al. (2020), in their study comparing surgery vs diet restriction, found that weight loss is the main driver of metabolic improvements seen after surgery. However, they did not investigate taste perception (103). Future longitudinal studies, using a control group for non-surgical weight loss, is required to confirm whether any detectable change in taste function is a result of the surgery itself, or whether this finding is a result of weight loss *per se*, or if it is due to a specific mechanism of bariatric surgery, and what this mechanism maybe by testing hypotheses around leptin.

6.7. Limitations

Limitations of the current study include not examining the impact of GOP on appetitive response to taste the stimuli of desire for fatty taste intensities that was found to change significantly in the post-operative period. Given that this infusion study ran for one-month, changes in sweet taste might need longer exposure to these hormones to make themselves apparent. The length of the visit and the consecutive taste tasks might contribute to sensory fatigue, which could be avoided by performing the tasks on consecutive days, but this would need more manpower and greater levels of supervision, which may conflict with the participants' work schedules and commitments. However, the use of direct measures of taste function could increase the validity of my findings.

7. CHAPTER SEVEN:

GENERAL DISCUSSION

Obesity is a significant problem, and bariatric surgery currently provides the most effective long-term management for obesity and diabetes, with RYGB being the gold standard surgery. It is not only leading to a significant weight loss and remission of diabetes in most patients, but also alters eating behaviour and taste preference toward healthier choices What is not known is whether these observed behavioural changes are underpinned by changes in reward-driven eating, whether these are sustained long term and how they compare with other weight-loss interventions. Therefore, in my thesis work, I compared eating behaviour in RYGB patients with those prescribed a Very Low-Calorie Diet (VLCD), matching the calorie intake of patients early after RYGB surgery and another group where we replicate the postprandial anorexigenic gut hormone changes seen after RYGB (GLP-1, OXM, PYY; referred to as GOP respectively) to explore the mechanism by which bariatric surgery works and use that knowledge to improve our understanding of obesity.

7.1. Summary of main findings

Taken together, these studies suggest that RYGB surgery was associated with a reduction in the reward drive to eat three-month post-surgery and that this was also maintained one-year after surgery. There was also a reduction in the other parameters such as external eating, (the drive to eat after seeing highly palatable food), a reduction in disinhibition (loss of control overeating), and a reduction in weight and shape concerns. These effects on eating behaviour were not replicated after one-month on calorie restriction (VLCD) or subcutaneous hormones infusion (GOP) suggesting that calorie restriction or gut hormones alone maybe not responsible for these changes in the reward drive to eat or eating behaviour following bypass. The only similarity between the surgical group and the hormonal infusion group was in the increase in the flexible dietary restraint measured by the Dutch Eating Behaviour questionnaire. Moreover,

the hormonal infusion group did not show any changes in the taste perception as observed following RYGB suggesting that gut hormones alone maybe not responsible for changes in taste observed following RYGB. This is the first study to comprehensively investigate the behavioural changes in more detail including comparing that with other weight loss interventions. Summary of main findings are summarised in (Table 29 on Page 260).

1- RYGB reduces reward drive to eat both acutely and in the long term in patients living with obesity and T2DM

The Power of Food Scale was used to investigate the impact of RYGB in reward drive to eat. The scale measures the reward drive to eat palatable food, rather than the actual consumption of palatable foods. My study showed that after RYGB, there was an acute (3 months) and chronic (1 year) reduction in reward-driven eating. This finding is in keeping with numerous behavioural and neuroimaging experiments in other studies (223, 292, 294, 407-419). For example, in a prospective observational study (411) that examined food reward systems using fMRI scans of 22 RYGB patients pre- and six months post-surgery, there was a reduction in BOLD response to high-calorie vs low-calorie food in the ventral tegmental area (VTA) at 6 months in the RYGB group, but not in the VSG or the normal-weight control group. There was also a greater reduction in the desire to eat highly palatable foods following RYGB compared to before, as well as in comparison to the control group, which was mirrored in brain activity patterns (411). The increased availability of palatable food was found to be an important trigger in stimulating food cravings, disrupting appetite regulation, and driving patterns of overeating in individuals living with obesity. In conclusion, the reduction in reward-drive to eat implies that following RYGB, individuals are less likely to be preoccupied with food or to be at risk of losing control and overeating, thus facilitating long-term changes in eating behaviour and hence a successful outcome.

2- The reduction in reward drive to eat in people living with obesity and T2DM following RYGB was not reflected in the VLCD or the GOP infusion

In contrast to the RYGB findings, there was no significant change in reward drive to eat measured by the PFS following one-month on the VLCD or the GOP infusion. Potential explanations for this could be that restriction of food alone (as in VLCD) or gut hormones alone (as in GOP) do not fully explain the efficacy of RYGB on eating behaviour or on reward-driven eating. Our group aims to further investigate this finding using functional MRI to measure direct changes to reward signalling to food in the brain reward centres in response to RYGB, VLCD and GOP. To investigate the impact of GOP on the neurology of the reward drive to consume highly palatable food, my team is currently in the process of analysing the fasting fMRI data we collected from participants during one-month on the GOP infusion and one-month on the VLCD. It would be interesting to compare the behavioural data that we have with the neuroimaging data to gain a better understanding of the impact of these three interventions (RYGB, VLCD, GOP) on the activation of the brain regions that are implicated in regulating appetite and food reward. This is the first time such a comparison has been made and these findings are therefore novel. Alternative explanations for the finding that the reward-driven eating was not altered in the VLCD and GOP group are that the discrepancy in the duration of the interventions (three months post-RYGB vs one-month on the VLCD or GOP), in the percentages of weight loss (18% post-RYGB vs 8% and 4% following VLCD and GOP respectively) may limit the conclusions that can be drawn due to lack of comparability between groups.

3- Flexible dietary restraint is increased to an equal extent following RYGB and GOP whereas rigid restraint is increased after VLCD

This study demonstrated that three months after RYGB and one-month after GOP an increase in dietary restraint was induced as measured by the DEBQ (flexible restraint). Dietary restraint

can be complex to interpret, and the concept of flexible restraint as measured by the DEBQ- A certain degree of flexible behavioural restraint seems to be necessary for successful weight-loss maintenance, and can protect individuals from disinhibited eating. However, drawing definite conclusions about dietary restraint based on existing research is unwise, because existing research is limited, and the measurement of dietary restraint is inconsistent.

One-month on the VLCD led to an increase in the restraint subscale of EDE-Q which measures rigid restraint. Rigid restraint is a behavioural attempt to maintain rigid control over dietary intake. This strategy relies on an all-or-nothing approach and is associated with eating disorder psychopathology and is often accompanied by dietary disinhibition when an emotional or external cue can act as a trigger (74). See Figure 1 on Page 24 for more details about the influence of restraint and disinhibition on obesity. In the VLCD study, participants were advised to restrict their intake to 800kcal/day using a meal replacement strategy so that the nature of the diet itself required a high level of rigid restrain, as opposed to the RYGB and GOP approach, where calorie intake was not limited. This is the likely explanation for the finding that VLCD was associated with rigid restraint whereas RYGB and GOP did not induce this.

4- RYGB surgery increases self-control in response to external eating cues and leads to reduction in weight and shape concerns; these findings were not replicated in the VLCD and GOP groups

This study showed a reduction in the effect of external stimuli – such as the sight or smell of food – post-RYGB but not post-VLCD or GOP. A reduction in weight and shape concerns following RYGB is expected after significant weight loss, and these findings were different to the post-VLCD or GOP results, where the weight loss was lower than post-RYGB weight loss. Interestingly, neither the VLCD nor the GOP infusion affected emotional or external eating at any time-point, suggesting that these interventions do not impact emotional or external eating.

Similarly, three months after RYGB there was no change in emotional eating, which contrasts with the findings in the literature, which suggest that despite the loss of reward from food measured by the PFS in the current study, RYGB patients may sometimes continue to use food for emotional regulation. In contrast to the findings of the current study, Pepino et al's study (2014, using the DEBQ) showed a significant reduction in emotional eating after surgery (269) and maintenance of this reduction for up to a year post-surgery (221). These discrepancies between the current findings and the literature are most likely due to the current study being underpowered because of the small number of participants. The study was powered for the clinical endpoints of glycaemia and weight loss.

5- RYGB surgery led to a reduction in dietary disinhibition which was not replicated in the other groups

Differences in external eating and disinhibition overeating may be explained by the reduction in food reward that was observed at the three-month point after RYGB and remained up to a year, but which were not observed after one-month on the VLCD or after the GOP infusion. There are three possible explanations for this: Firstly, a reduction in reward-driven eating may lead to behavioural changes such as a reduction in dietary disinhibition and external eating, which may facilitate weight loss after RYGB surgery. Although external eating and the availability of palatable food were found to be important trigger in stimulating food intake (457, 633), the link between reward-driven eating and disinhibition or external eating need more in-depth investigations. An alternative explanation is that a reduction in external eating might support the reduction of disinhibition. The definition of disinhibition does support that assumption. It is defined as a loss of control leading to overeating and eating opportunistically in response to external cues (479). Higher disinhibition levels were found to be associated in women with an increase in sweet food consumption during stressful times (482). A third possible explanation is that the duration of the VLCD or GOP approaches (one-month) was not

enough to show a significant change in dietary disinhibition in comparison to three months post-RYGB.

6- There was an improvement of general health and health-related quality of life after RYGB

The current study showed a general improvement in quality of life three months after RYGB, a result that matches previous studies demonstrating consistent improvements in weight- and health-related quality of life after bariatric surgery, measured using the IWQOL and SF-36 questionnaires, respectively. The most significant improvements in my study in terms of health-related quality of life were in the areas of pain and physical functionality. In the current study, improvements in these domains were apparent, as well as improvements in participants' sexual lives after RYGB surgery. Improvements in HR-QoL post-gastric bypass could be expected due to a reduction in excess body weight and diminishing obesity-specific symptoms. Unexpectedly, health-related quality of life did not change after one-month on the VLCD or after it, despite the significant weight loss that was achieved post-VLCD and GOP. The current findings might be explained by the fact that the VLCD participants in this study were in better psychological and physical shape before the intervention than the surgical group. Another suggestion would be that patients who actively look for obesity treatment or gastric bypass surgery candidates might be more sensitive about their weight and experience worse quality of life as a result than those who are simply participating in a weight-loss study. The final possible explanation for this difference could be due to the fact that this study was underpowered and of short duration in terms of the VLCD participants (one-month) compared to other studies.

7- RYGB, VLCD, and GOP did not change the mood or psychological characteristics of participants

The current findings show no significant post-GOP infusion changes in impulsivity, reward sensitivity (reward responsiveness, reward drive, hedonic or behavioural inhibition), levels of

depression and anxiety as measured using the Barratt Impulsiveness Scale, the Behavioural Activation and Inhibition Scale (BIS/BAS), or the Beck Depression Inventory-II and Hospital Anxiety and Depression Scale (HADS). Many of these traits are considered common among patients with obesity (491), and have an impact on eating behaviour and contribute to limited weight loss after bariatric surgery. At a behavioural level, impulsive people, i.e. those who are unable to resist an immediate reward instead of waiting for a more significant longer-term reward (492), are more likely to eat high-calorie foods (493). Reviews show that patients with obesity – particularly those who seek bariatric surgery – tend to show higher levels of impulsivity and associated neurological problems (494-496). This was in line with previous findings that reported depression (491) and impulsivity (497) as common problems among people who live with obesity. Symptoms of depression were found to improve when weight loss was achieved (277, 498, 499). The discrepancy between the current results and the literature is most likely due to the minimum scores in impulsivity and depression before the surgery and throughout the trial period, which contrasts with previous reports. It may also be due to the current study may be insufficiently powerful to detect the change in psychological characteristics as the study was powered for the clinical endpoints of glycaemia and weight loss. Therefore, further research is needed to make definitive statements about the impact of RYGB, VLCD and GOP on these measured factors.

8- RYGB, VLCD, and GOP reduced dietary intake equally but did not change alcohol consumption

All three interventions (RYGB, VLCD, and GOP) led to a reduction in body weight and a significant reduction in food intake with no change in macronutrient distribution. However, all three interventions did not show any significant changes in alcohol intake at any time point. This is in keeping with other studies which show later but not acute changes in alcohol use disorder frequency.

9- Gut hormones are unlikely to be responsible for the effect of RYGB on sweet taste detection, intensity and consummatory reward

The current findings showed that a subcutaneous GOP infusion over a month, with target doses that mimicked the postprandial post-RYGB GOP level for 10-12 hours a day, did not affect on patients' taste functions. The functions tested included sensory-discriminative components (taste detection thresholds and intensity) and reward components (just about right scores and gLMS ratings for sucrose) in patients with obesity and T2DM, compared with the control group. GOP infusion did not affect the sensory or reward domains of sweet taste function in patients with obesity and T2DM compared with the control group.

7.2. Concluding Comments

The findings of this study emphasize some of the behavioural differences in the mechanisms that underlie the success of RYGB in the treatment of obesity over dietary restriction (VLCD) or gut hormone infusion (GOP). These differences are based on reductions in reward eating, dietary disinhibition, external eating and weight and shape concerns that were observed at three-month after RYGB but not replicated after one-month on VLCD or gut hormones infusion (GOP) suggesting that calorie restriction or gut hormones maybe not be responsible for the change in eating behaviour following RYGB.

Although previous work on the effects of Octreotide in reducing food reward, including activation in the *nucleus accumbens* to food pictures in RYGB patients, supports the hypothesis that gut hormones may mediate reward post-RYGB changes in appetite, the findings of this study do not support this hypothesis.

In a comparison of RYGB and GOP as treatments for obesity, we can conclude that both approaches increased dietary restraint, but altered food reward responses differently, as assessed by the DEBQ and PFS respectively and result in different degrees of weight loss. VLCD succeeded in achieving a weight loss of more than 5% but produced no change in the

reward drive to eat and increased the rigid restraint mechanisms measured by the EDE scale. This study is the first to make use of such a comprehensive set of questionnaires to assess eating behaviour, the reward drive to eat and psychological changes following three different weight-loss interventions (RYGB, VLCD and GOP). Further neuroimaging studies are needed to clarify the role of GOP and VLCD in food reward and to support the behavioural findings in this study. The investigation of other potential mechanisms, such as bile acids and the post-ingestive effects of high-fat and sweet foods as potential mediators for the lower reward response to food seen in post-RYGB patients will accelerate the development of more effective, cheaper, and safer non-surgical treatments for obesity.

Some of the strengths of this study, including profiling by means of a set of different questionnaires that each measure a different set of parameters such as eating behaviour and psychological state of mind, are found to be related to the success or failure of weight loss programmes. This study is the first to compare three different dietary interventions (surgical, dietary and gut hormone infusion) using similar baseline criteria. The study was fairly robust in its exclusion criteria. However, the study had limitations, including the inconsistency in timescales used to assess different responses and the small cohort size, which may have led to the study being underpowered. In the RYGB group, the first assessment took place three months post-RYGB, but the assessments were done after one-month for the VLCD and GOP groups. As a result of this, different levels of weight loss were observed, which might influence the current findings. Discrepancies in results are most likely due to the current study being underpowered because of the small number of participants.

7.3. Conclusion

RYGB surgery is associated with a reduction in reward drive to eat and alteration in some eating behaviour such as eating restraint, external eating, and disinhibition which might be facilitating long-term weight loss and maintenance. These changes might be mediated by

various changes in the neural networks that control homeostatic and reward drive to eat rather than the calorie restriction or the augmentation of anorexigenic gut hormones (GOP) alone. Further studies with larger samples are warranted to confirm these findings and to assist with the development of new treatments and personalised therapeutic approaches to improve treatment outcomes.

Table 29: *Summary of findings*

	RYGB	VLCD	GOP	Saline
The Dutch Eating Behaviour Questionnaire (DEBQ)				
• **Dietary Restraint (score/5)**	↑	—	↑↑	—
• **Emotional eating (score/5)**	—	—	—	—
• **External eating (score/5)**	↓	—	—	—
Three-Factor Eating Questionnaire (TFEQ)				
• **Cognitive Restraint (score/21)**	—	—	—	—
• **Disinhibition (score/16)**	↓↓	—	—	—
• **Hunger (score/14)**	—	—	—	—
Eating Disorder Examination Questionnaire (EDEQ)				
• **Restraint**	—	↓	—	—
• **Weight**	↓↓	—	—	—
• **Eating**	—	—	—	—
• **Shape**	↓↓	—	—	—
• **Global**	—	—	—	—
Food Reward Questionnaire				
• **Power of Food Scale**	↓↓	—	—	—
Psychological Traits				
• **Barratt Impulsiveness Scale**	—	—	—	↓
Behavioural Inhibition System/Behavioural Activation System (BIS/BAS) Scales				
• **Drive-Seeking**	—	—	—	—
• **Fun-Seeking**	—	—	—	—
• **Reward-Responsiveness**	—	—	—	—
• **BAS**	—	—	—	—
Hospital Anxiety and Depression Scale				
• **HADS-Anxiety**	—	—	—	—
• **HADS-Depression**	—	—	—	—
• **BDI-II**	—	—	—	—
• **Alcohol Audit**	—	—	—	—
SF-36TM Health Survey (SF-36)				
• **Physical Functioning**	↑↑	—	—	—
• **Limitations due to physical health**	↑	—	—	—
• **Limitations due to emotional problems**	↑↑	—	—	—
• **Energy/Fatigue**	—	—	—	—

• **Emotional well-being**	—	—	—	—
• **Social Functioning**	—	—	—	—
• **Pain**	↑↑	—	—	—
• **General Health**	↑	—	—	—
Quality-of-Life Questionnaire (IWQoL-Lite)				
• **Physical Function**	↑	—	—	↓↓
• **Self-Esteem**	—	↑	—	—
• **Sexual Life**	—	—	—	—
• **Public Distress**	—	—	—	—
• **Work Problems**	—	↑	—	—
• **IWQoL Total**	↑↑	—	—	—
Food Intake				
• **Total calorie intake (kcal/day)**	↓↓	↓	↓↓	—
• **Carbohydrate Intake (%)**	—	—	—	—
• **Protein Intake (%)**	—	—	—	—
• **Fat Intake (%)**	—	—	—	—
• **Alcohol Intake (%)**	—	—	—	—

↑: Short-term increase; ↑↑: Lomg-term increase; —: No changes; ↓: Short-term reduction; ↓↓: Lomg-term reduction

7.4. Limitations and future directions

This is the first time such a comparison of three different interventions (surgery [RYGB], meal replacement [VLCD], and gut hormones infusion [GOP]) has been made, and its preliminary findings are therefore unique. However, limitations remain and need to be considered in interpreting the results.

7.4.1. Larger longitudinal studies

The number of participants in this study was small, implying a high risk of type-I statistical error. The study may therefore be underpowered in terms of making definitive statements about the impact of the three interventions on the measured factors. Moreover, there is a possibility of selection bias, which could decrease the representativeness of the study samples. Even though all the three interventions followed the same eligibility criteria that reflected my target population, the VLCD and GOP participants were selected via advertisements (probability sampling) and the RYGB participants were selected from the waiting list for bariatric surgery (non-probability sampling), which increases the risk of potential selection bias, as patients seeking and undergoing bariatric surgery might be more motivated and may behave in a different way than those who chose to participate in a study. Future large-scale studies are needed to replicate the results of this thesis with longer follow-up times, whilst avoiding the limitations inherent in this study to provide new insights into the mechanisms underlying the findings shown here. Having observed a long-term reduction in reward response to food in patients who underwent RYGB surgery that was not seen in patients who followed VLCD or received a GOP infusion, future studies should aim to confirm this. Looking for biological markers of change in reward drive to eat following RYGB would also be necessary in order to gain a better understanding of the impact of these three interventions (RYGB, VLCD, GOP) on the reward drive to eat that are implicated in regulating appetite.

7.4.2. Comparison of behavioural data with neuroimaging data

To add a new aspect to this study and explore prior findings in greater length, my team is currently in the process of analysing the fasting fMRI data we collected from participants during each intervention. It would be interesting to compare the behavioural data that we collected from the questionnaires with the neuroimaging data. The reduction in food reward is perhaps in part responsible for the other changes in eating behaviour observed in this thesis such as disinhibition, external and restraint eating.

7.4.3. Using qualitative questioners

These findings were obtained using quantitative self-reporting questionnaires. No individual follow-up interviews were undertaken, and no other observations were made. Conducting a small qualitative study would therefore be a useful addition to the literature in this area because it is difficult to capture behavioural details and identify differences between individuals with quantitative studies. There is not enough literature in this area currently, and qualitative studies would tell us a great deal more. If we have done that from the beginning it might have helped to guide us with the questionnaires, and we might have been able to narrow down the questionnaires used. Moreover, one of the limitations of this study is that patients with eating disorders were not included in it, and it might be useful to look specifically at people with eating disorders or food addiction to understand how such factors would affect this group of patients.

7.4.4. Use of biological markers to validate self-reported dietary intake

One of the study limitations involved the use of food diaries to assess calories and macronutrient intake. Although this is a commonly used approach in free-living studies, the underreporting of caloric intake is a significant problem in obesity studies (515, 516). Using food diaries as part of dietary assessment is prone to selection bias and may not work as a direct assessment of measuring energy intake and food preferences (517, 518). Participants may

select some foods to report and ignore the rest, making their reports open to accusations of objectivity. Using more objective methods to measure food intake, such as biomarkers of intake including urinary nitrogen excretion, may add a potentially valuable source of accuracy to overcome the limitation of using food diaries.

7.4.5. Further investigation of other RYGB mechanisms

This study was the first time that a combination of three anorexic hormones (GOP), known to be augmented after RYGB, have been used together subcutaneously in patients with obesity and type 2 diabetes to measure the changes in eating behaviour, reward eating and taste function. Further studies are needed to clarify the role of these gut hormones, as well as other factors such as bile acids and post-ingestive effects of high-fat and sweet foods as potential mediators for the lower reward response to food seen in RYGB. In addition, the in-depth interrogation of the mechanisms underlying this, and other potential mechanisms will accelerate development interventions that directly target food reward and other eating behaviour such as external eating. Meanwhile, this study did not examine the impact of GOP on appetitive response to taste or the stimuli of desire for fatty taste intensities that was found to change significantly in the post-operative period. Given that this infusion study ran for only one-month, changes in sweet taste might need longer exposure to these hormones to make themselves felt. Further study is warranted to overcome the limitations of the current study and to determine whether VLCD or GOP is involved in changes in eating behaviour or reward drive seen after RYGB.

The work presented in this thesis could be used as a platform to design future studies to further reinforce our understanding of the role and effects of RYGB surgery on eating behaviour and reward eating. Further research may also be able to assess whether the change is influence by the elevated levels of gut hormones post-RYGB – especially by addressing some of the limitations of the current study.

7.5. The importance of language in the field of obesity

Language is a simple but powerful tool that should be considered when helping patients manage their health. Feldman et al. reported that language has an impact on attitudes, opinions and behavioural intentions toward individuals with disabilities, diseases or health conditions (634). Language reveals how medical professionals and primary care providers judge and make sense of their patients and their struggles, and this impacts the quality of patient care and treatment outcomes (635-638). In the field of obesity, labelling individuals with their disease by referring to them as "obese" or using stigmatizing language such as "fat" are shown to have a negative impact on how individuals with obesity feel about their condition and how likely they are to seek medical care or disengage from the provider, and perpetuates the already pervasive stigma attached to weight issues (639). When asked how participants would react if they felt stigmatized by their doctor about their body weight, 19% reported that they would avoid future medical appointments, while 21% would seek a new doctor (640). Despite the best intentions, there is a weight-related stigma among healthcare providers toward patients living with obesity (641-644). The concept of adopting person-first expressions for obesity that entails referring to a medical condition as a noun rather than an adjective is recommended – not only among healthcare providers but also within medical and scientific communities and the community as a whole. This is the standard for addressing people with chronic disease respectfully. For instance, rather than saying "obese patients" it is better to say "patients living with obesity" and the term "severe obesity" is preferred over "morbid obesity" (645). The word "obese" when used as an adjective does not distinguish the patient from the condition, and instead uses the condition as a form of identity. Another reason against using terms like "obese," "fat" and "extremely obese" is because studies show that patients find these phrases derogatory and personally offensive, and generally comprise their least-chosen terms for describing weight issues. They generally prefer more neutral, less stigmatizing and motivating

terms, such as “weight” or “BMI” (638, 646, 647). The APA Style Manual has adopted people-first language for most chronic diseases and disabilities and in all publications to avoid labelling patients by their illness. Moreover, the members of the Obesity Care Continuum and the Obesity Society for Metabolic and Bariatric Surgery have emphasized using people-first language as the standard in all publications and presentations (639). Despite the growing advocacy for people-first language usage, such usage has not been widely adopted for obesity. In published studies, these differences in standards are readily apparent. Searching for research publications in Google Scholar using the phrase “hypertensive people” yields 7,970 results, while searching for “people with hypertension” yields 16,400 results. The same norm appears with diabetes, but the opposite is true in obesity. Searching for the phrase “people with obesity” yields 12,100 results, while searching for “obese people” yields 75,500 results. Patients may be less willing to consider treatment if they believe that the weight issue is entirely their fault, and that they just need to “try harder”, as such attitudes promote weight stigma and prevent them from seeking other treatments options such as bariatric surgery. Focusing on the genetic, biological and environmental factors in their resistance to treatment of obesity rather than personal or moral failings have been demonstrated to reduce stigma, improve treatment utilisation and encourage greater medical coverage and access. An example of using people-first language in the current thesis was in using the phrase “the reward drive to eat/ reward-driven eating” instead of “hedonic eating” which has been used in several studies before (648-652). The meaning of the word “hedonic”, according to the Oxford Dictionary (653) is “relating to or characterized by hedonism”. When the term “hedonism” first appeared in English in the mid-nineteenth century, it referred to the ideas of ancient Greek philosophers (such as the Epicureans) who believed that happiness or pleasure was the most important objective in life. The word “hedonism” has a judgemental connotation in today’s society. If someone is described as hedonistic, they are thought to gain their happiness through selfishness and giving

in to impulses rather than concentrating on health, teamwork or family time or their occupations. Hedonism is derived from the Greek word hēdonē ("pleasure"), which is also the root of anhedonia ("a psychological condition marked by the inability to perceive pleasure in ordinarily pleasurable acts") (653).

In summary, the awareness of the problem is the first step toward identifying strategies to improve care for patients with obesity. There is a need for more training on talking to patients and research study participants to identify individuals' language preferences to ensure that the power of language is used to eliminate stereotypes, reduce the stigma associated with obesity and to promote rather than hinder better levels of understanding and patient care. Encouraging research papers to use people-first language toward obesity as a prerequisite for publication would help to reduce the stigma associated with this disease and further eradicate weight bias, while fully respecting the people affected and working towards improving their health outcomes.

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Appendices

Appendix (1) : **Information sheet for research participants**

Appendix (2) : **Participant consent form**

Appendix (3) : **Dutch Eating Behaviour Questionnaire**

Appendix (4) : **Three-Factor Eating Questionnaire**

Appendix (5) : **Eating Disorder Examination Questionnaire**

Appendix (6) : **Power of Food Scale**

Appendix (7) : **The Beck Depression Inventory (BDI-II)**

Appendix (8) : **Behavioural Inhibition and Activation System (BIS/BAS) scales**

Appendix (9) : **Barratt Impulsivity Scale**

Appendix (10) : **Hospital Anxiety and Depression Scale (HADS)**

Appendix (11) : **Impact of Weight on Quality of Life-Lite (IWQOL-Lite)**

Appendix (12) : **Short-Form 36 Health Survey Questionnaire (SF36)**

Appendix (13) : **Alcohol Use Disorders Identification Test (AUDIT)**

Appendix (14) : **Dietary food record**

Appendix (15) : **Cup arrangements and scoring Sheets for Sweet Taste Detection test**

Appendix (16) : **The Intensity generalised labelled magnitude scale (gLMS)**

Appendix (17) : **The Consummatory Taste Reward Scales**

Appendix (18) : **gLMS Hedonic scale**

Appendix (19) : **Intensity Scale**

Appendix (1) : Information sheet for research participants

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Ref. No. 13/LO/1510 Version 08 Submission date: 11th of December 2017

INFORMATION SHEET FOR RESEARCH PARTICIPANTS (RYGB group)

You will be given a copy of this information sheet and a signed copy of your consent form to keep, should you decide to participate in the study.

Do gut hormones mediate the beneficial effects of Roux-en-Y bypass surgery?

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

If you do decide to take part, please let us know beforehand if you have been involved in any other study during the last year. You are free to withdraw at any time without explanation. Please be assured that if you decide not to take part this will not affect your clinical care in any way.

Thank you for reading this.

WHAT IS THE PURPOSE OF THE STUDY?

Roux-en-Y gastric bypass (RYGB) is an operation that helps people lose weight. In those with diabetes it can also produce an immediate and long-lasting improvement in blood sugar control. We do not yet fully understand how the operation produces these beneficial effects.

We have observed that after the operation, blood levels of three natural hormones – glucagon like peptide-1 (GLP-1), oxyntomodulin (OXM) and Peptide YY (PYY) – are increased. This study will look at whether the higher levels of these hormones after surgery actually cause the improvement in blood sugars and weight loss that is achieved. We will compare patients who have undergone RYGB surgery with a non-operated group, who will receive long-term treatment with a hormone infusion instead. We will be comparing both of these groups to another group of patients, who will undergo an intensive low calorie diet under the supervision of a specialist dietician. We need to understand whether dieting alone produces the same beneficial effects as RYGB, or whether there are some extra benefits that arise from the altered hormone profile.

You have been selected to enter the study because you have chosen to undergo RYGB surgery. We hope to use this information to help us develop non-surgical anti-obesity treatments in the future.

WHY HAVE I BEEN CHOSEN?

Individuals who are eligible for RYGB on the NHS are being recruited to take part in this study. You have already been referred for this type of surgery based on your weight and you may also have a diagnosis of diabetes. We are recruiting a group of patients who would have undergone this surgery anyway, in whom we will perform a much more intensive follow up. From the few weeks running up to your operation and for up to one year after, we will be inviting you to our research unit to undergo regular tests to help us understand much more clearly why this operation is so successful at helping people lose weight and improve their blood sugar control.

Appendix (2) : Participant consent form

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Do gut hormones mediate the beneficial effects of Roux-en-Y bypass surgery? (PARTICIPANT CONSENT FORM – GROUP A)

The participant should complete the whole of this sheet him- or herself (please initial each statement if it applies to you)

I have read the Information Sheet for Research Participants in the Roux-en-Y bypass surgery arm of the study, Version 07, dated 22nd of April 2016.	☐
I have been given the opportunity to ask questions and discuss this study	☐
I have received satisfactory answers to all my questions	☐
I have received enough information about the study	☐
The study has been explained to me by Dr	☐
I understand that I am free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting my future medical care	☐
I agree to take part in this study	☐
I agree that my GP will be informed that I am taking part in the study	☐
I understand that the NHS and College as sponsor may also review records as part of audit process	☐
I agree that my blood samples will be kept indefinitely and may be used for further analysis or in other ethically approved research	☐

Appendix (3) : Dutch Eating Behaviour Questionnaire

1. If you have put on weight, do you eat less than you usually do?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

2. Do you try to eat less at mealtimes than you would like to eat?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

3. How often do you refuse food or drink offered because you are concerned about your weight?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

4. Do you watch exactly what you eat?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

5. Do you deliberately eat foods that are slimming?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

6. When you have eaten too much, do you eat less than usual the following days?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

7. Do you deliberately eat less in order not to become heavier?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

8. How often do you try not to eat between meals because you are watching your weight?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

9. How often in the evening do you try not to eat because you are watching your weight?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

10. Do you take into account your weight with what you eat?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

11. Do you have the desire to eat when you are irritated?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

12. Do you have a desire to eat when you have nothing to do?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

13. Do you have a desire to eat when you are depressed or discouraged?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

14. Do you have a desire to eat when you are feeling lonely?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

15. Do you have a desire to eat when somebody lets you down?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

16. Do you have a desire to eat when you are cross?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

17. Do you have a desire to eat when you are approaching something unpleasant to happen?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

18. Do you get the desire to eat when you are anxious, worried or tense?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

19. Do you have a desire to eat when things are going against you or when things have gone wrong?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

20. Do you have a desire to eat when you are frightened?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

21. Do you have a desire to eat when you are disappointed?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

22. Do you have a desire to eat when you are bored or restless?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

23. Do you have a desire to eat when you are emotionally upset?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐ Not Relevant ☐

24. If food tastes good to you, do you eat more than usual?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

25. If food smells and looks good do you eat more than usual?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

26. If you see or smell something delicious, do you have the desire to eat it?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

27. If you have something delicious to eat, do you eat it straight away?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

28. If you walk past the baker do you have the desire to buy something delicious?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

29. If you walk past a snack bar or a café, do you have the desire to buy something delicious?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

30. If you see others eating, do you also have the desire to eat?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

31. Can you resist eating delicious foods?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

32. Do you eat more than usual, when you see others eating?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

33. When preparing a meal are you inclined to eat something?

Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often ☐

Appendix (4) : Three-Factor Eating Questionnaire

THE THREE-FACTOR EATING QUESTIONNAIRE
Please circle the response that you feel best describes you

Part 1	True	False
1. When I smell a sizzling steak or see a juicy piece of meat, I find it very difficult to keep from eating, even if I have just finished a meal.	**T**	**F**
2. I usually eat too much at social occasions, like parties and picnics.	**T**	**F**
3. I am usually so hungry that I eat more than three times a day.	**T**	**F**
4. When I have eaten my quota of calories, I am usually good about not eating any more.	**T**	**F**
5. Dieting is so hard from me because I just get too hungry.	**T**	**F**
6. I deliberately take small helpings as a means of controlling my weight.	**T**	**F**
7. Sometimes things just taste so good that I keep on eating even when I am no longer hungry.	**T**	**F**
8. Since I am often hungry, I sometimes wish that while I am eating, an expert would tell me that I have had enough or that I can have something more to eat.	**T**	**F**
9. When I feel anxious, I find myself eating.	**T**	**F**
10. Life is too short to worry about dieting.	**T**	**F**
11. Since my weight goes up and down, I have gone on reducing diets more than once	**T**	**F**
12. I often feel so hungry that I just have to eat something.	**T**	**F**
13. When I am with someone who is overeating, I usually overeat too.	**T**	**F**
14. I have a pretty good idea of the number of calories in common food.	**T**	**F**
15. Sometimes when I start eating, I just can't seem to stop.	**T**	**F**
16. It is not difficult for me to leave something on my plate.	**T**	**F**
17. At certain times of the day, I get hungry because I have gotten used to eating then.	**T**	**F**
18. While on a diet, if I eat food that is not allowed, I consciously eat less for a period of time to make up for it.	**T**	**F**
19. Being with someone who is eating often makes me hungry enough to eat also.	**T**	**F**
20. When I feel blue, I often overeat.	**T**	**F**
21. I enjoy eating too much to spoil it by counting calories or watching my weight.	**T**	**F**
22. When I see a real delicacy, I often get so hungry that I have to eat right away.	**T**	**F**
23. I often stop eating when I am not really full as a conscious means of limiting the amount that I eat.	**T**	**F**
24. I get so hungry that my stomach often seems like a bottomless pit.	**T**	**F**
25. My weight has hardly changed at all in the last ten years.	**T**	**F**
26. I am always hungry, so it is hard for me to stop eating before I finish that food on my plate.	**T**	**F**
27. When I feel lonely, I console myself by eating.	**T**	**F**
28. I consciously hold back at meals in order not to gain weight.	**T**	**F**
29. I sometimes get very hungry late in the evening or at night.	**T**	**F**
30. I eat anything I want, any time I want.	**T**	**F**
31. Without even thinking about it, I take a long time to eat.	**T**	**F**
32. I count calories as a means of controlling my weight.	**T**	**F**
33. I do not eat some foods because they make me fat.	**T**	**F**
34. I am always hungry enough to eat at any time.	**T**	**F**
35. I pay a great deal of attention to changes in my figure.	**T**	**F**
36. While on a diet, if I eat a food that is not allowed, I often then splurge and eat other high calorie foods.	**T**	**F**

Continued: Three-Factor Eating Questionnaire

THE THREE-FACTOR EATING QUESTIONNAIRE

Part II				
37. How often are you dieting in a conscious effort to control your weight?	Rarely	sometimes	usually	always
38.Would a weight fluctuation of 5 lbs (2¼ kg) affect the way you live your life?	not at all	slightly	moderately	very much
39.How often do you feel hungry?	only at mealtimes	sometimes between meals	Often between meals	almost always
40.Do your feelings of guilt about overeating help you to control your food intake?	Never	rarely	often	always
41.How difficult would it be for you to stop eating halfway through dinner and not eat for the next four hours?	Easy	slightly difficult	moderately difficult	very difficult
42.How conscious are you of what you are eating?	not at all	slightly	moderately	extremely
44.How frequently do you avoid 'stocking up' on tempting foods?	Almost never	seldom	usually	Almost always
45.How likely are you to shop for low calorie foods?	Unlikely	slightly unlikely	Moderately unlikely	very likely
46.Do you eat sensibly in front of others and splurge alone?	Never	rarely	often	always
47.How likely are you to consciously eat slowly in order to cut down on how much you eat?	Unlikely	slightly unlikely	moderately unlikely	very likely
48. How frequently do you skip dessert because you are no longer hungry?	almost never	seldom	at least once a week	Almost every day
49. How likely are you to consciously eat less than you want?	Unlikely	slightly likely	moderately likely	very likely
50. Do you go on eating binges though you are not hungry?	Never	rarely	sometimes	at least once a week

51. On a scale of 0 to 5, where 0 means no restraint (eating whatever you want, whenever you want it) and 5 means total restraint constantly limiting food intake and never 'giving in'), what number would you give yourself?	0	1	2	3	4	5
	eat whatever you want, whenever you want it	usually eat whatever you want, whenever you want it	often eat whatever you want, whenever you want it	often limit food intake, but often 'give in'	usually limit food intake, rarely 'give in'	constantly limiting food intake, never 'giving in'

52. To what extent does this statement describe your eating behaviour? 'I start dieting in the morning, but because of any number of things that happen during the day, by evening I have given up and eat what I want, promising myself to start dieting again tomorrow'	not like me	little like me	pretty good description of me	describes me perfectly

Appendix (5) : Eating Disorder Examination Questionnaire (EDE_Q)

EATING QUESTIONNAIRE

Instructions: The following questions are concerned with the past four weeks (28 days) only. Please read each question carefully. Please answer all of the questions. Thank you.

Questions 1 to 12: Please circle the appropriate number on the right. Remember that the questions only refer to the past four weeks (28 days) only.

.

	On how many of the past 28 days	No days	1-5 days	6-12 days	13-15 days	16-22 days	23-27 days	Every day
1	Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
2	Have you gone for long periods of time (8 waking hours or more) without eating anything at all in order to influence your shape or weight?	0	1	2	3	4	5	6
3	Have you tried to exclude from your diet any foods that you like in order to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
4	Have you tried to follow definite rules regarding your eating (for example, a calorie limit) in order to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
5	Have you had a definite desire to have an empty stomach with the aim of influencing your shape or weight?	0	1	2	3	4	5	6
6	Have you had a definite desire to have a totally flat stomach?	0	1	2	3	4	5	6
7	Has thinking about food, eating or calories made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?	0	1	2	3	4	5	6
8	Has thinking about shape or weight made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?	0	1	2	3	4	5	6
9	Have you had a definite fear of losing control over eating?	0	1	2	3	4	5	6
10	Have you had a definite fear that you might gain weight?	0	1	2	3	4	5	6
11	Have you felt fat?	0	1	2	3	4	5	6
12	Have you had a strong desire to lose weight?	0	1	2	3	4	5	6

Continued: Eating Disorder Examination Questionnaire (EDE_Q)

Questions 22 to 28: Please circle the appropriate number on the right. Remember that the questions only refer to the past four weeks (28 days).

	Over the past 28 days …..	Not at all		Slightly		Moderate -ly		Markedly
22	Has your weight influenced how you think about (judge) yourself as a person?	0	1	2	3	4	5	6
23	Has your shape influenced how you think about (judge) yourself as a person?	0	1	2	3	4	5	6
24	How much would it have upset you if you had been asked to weigh yourself once a week (no more, or less, often) for the next four weeks?	0	1	2	3	4	5	6
25	How dissatisfied have you been with your weight?	0	1	2	3	4	5	6
26	How dissatisfied have you been with your shape?	0	1	2	3	4	5	6
27	How uncomfortable have you felt seeing your body (for example, seeing your shape in the mirror, in a shop window reflection, while undressing or taking a bath or shower)?	0	1	2	3	4	5	6
28	How uncomfortable have you felt about others seeing your shape or figure (for example, in communal changing rooms, when swimming, or wearing tight clothes)?	0	1	2	3	4	5	6

What is your weight at present? (Please give your best estimate.) .....

What is your height? (Please give your best estimate.) .....

If female: Over the past three-to-four months have you missed any menstrual periods? .....

If so, how many? .....
Have you been taking the "pill"? .....

THANK YOU

Appendix (6) : Power of Food Scale

Please indicate the extent to which you agree that the following items describe you. Use the following scale from 1-5 in your responses.

I don't agree (1)	I agree a little (2)	I agree somewhat (3)	agree quite a bit (4)	I strongly agree (5)

1. I find myself thinking about food even when I am not physically hungry

   (1) (2) (3) (4) (5)

2. I get more pleasure from eating than I do from almost anything else

   (1) (2) (3) (4) (5)

3. If I see or smell a food I like, I get a powerful urge to have some

   (1) (2) (3) (4) (5)

4. When I'm around a fattening food I love, it's hard to stop myself from at least tasting it

   (1) (2) (3) (4) (5)

5. It's scary to think of the power that food has over me

   (1) (2) (3) (4) (5)

6. When I know a delicious food is available, I can't help myself from thinking about having some

   (1) (2) (3) (4) (5)

7. I love the taste of certain foods so much that I can't avoid eating them even if they're bad for me

   (1) (2) (3) (4) (5)

8. Just before I taste a favourite food I feel intense anticipation

   (1) (2) (3) (4) (5)

9. When I eat a delicious food I focus a lot on how good it tastes

   (1) (2) (3) (4) (5)

10. Sometimes, when I'm doing everyday activities, I get an urge to eat "out of the blue" (for no apparent reason)

(1) (2) (3) (4) (5)

11. I think I enjoy eating a lot more than most other people

(1) (2) (3) (4) (5)

12. Hearing someone describe a great meal makes me really want to have something to eat

(1) (2) (3) (4) (5)

13. It seems like I have food on my mind a lot

(1) (2) (3) (4) (5)

14. It's very important to me that the foods I eat are as delicious as possible

(1) (2) (3) (4) (5)

15. Before I eat a favourite food my mouth tends to flood with saliva

(1) (2) (3) (4) (5)

Appendix (7) : The Beck Depression Inventory (BDI-II)

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____

Page 14 patient inits: _____

Baseline

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

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Subtotal Page 1

Continued on Back

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Continue: The Beck Depression Inventory (BDI-II)

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____

Page 15

Baseline

patient inits: _____

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

3 4 5 6 7 8 9 10 11 12 A B C D E

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

NR15645

Appendix (8) : Behavioural Inhibition and Activation System (BIS/BAS) scales

For each item, indicate how much you agree or disagree with what the item says

N°	Question	Very true for me	Somewhat true for me	Somewhat false for me	Very false for me
1.	A person's family is the most important thing in life.				
2.	Even if something bad is about to happen to me, I rarely experience fear or nervousness.				
3.	I go out of my way to get things I want.				
4.	When I'm doing well at something, I love to keep at it.				
5.	I'm always willing to try something new if I think it will be fun.				
6.	How I dress is important to me.				
7.	When I get something I want, I feel excited and energized.				
8.	Criticism or scolding hurts me quite a bit.				
9.	When I want something I usually go all-out to get it.				
10.	I will often do things for no other reason than that they might be fun.				
11.	It's hard for me to find the time to do things such as get a haircut.				
12.	If I see a chance to get something I want I move on it right away.				
13.	I feel pretty worried or upset when I think or know somebody is angry at me.				
14.	When I see an opportunity for something I like I get excited right away.				
15.	I often act on the spur of the moment.				
16.	If I think something unpleasant is going to happen I usually get pretty worked up.				
17.	I often wonder why people act the way they do.				
18.	When good things happen to me, it affects me strongly.				
19.	I feel worried when I think I have done poorly at something important.				
20.	I crave excitement and new sensations.				
21.	When I go after something I use a no holds barred approach.				
22.	I have very few fears compared to my friends.				
23.	It would excite me to win a contest.				
24.	I worry about making mistakes.				

Appendix (9) : Barratt Impulsivity Scale

Directions: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much on any statement. Answer quickly and honestly.				
	Rarely/Never	Occasionally	Often	Almost/Always
1) I plan tasks carefully.				
2) I do things without thinking.				
3) I make-up my mind quickly.				
4) I am happy-go-lucky.				
5) I don't "pay attention."				
6) I have "racing" thought.				
7) I plan trips well ahead of time.				
8) I am self-controlled.				
9) I concentrate easily.				
10) I save regularly.				
11) I "squirm" at plays or lectures.				
12) I am a careful thinker.				
13) I plan for job security.				
14) I say things without thinking.				
15) I like to think about complex problems.				
16) I change jobs.				
17) I act "on impulse".				
18) I get easily bored when solving thought problems.				
19) I act on the spur of the moment.				
20) I am a steady thinker.				
21) I change residences.				
22) I buy things on impulse.				
23) I can only think about one thing at a time.				
24) I change hobbies.				
25) I spend or charge more than I earn.				
26) I often have extraneous thoughts when thinking.				
27) I am more interested in the present than the future.				
28) I am restless at the theatre or lectures.				
29) I like puzzles.				
30) I am future oriented.				

Appendix (10) : Hospital Anxiety and Depression Scale (HADS)

Clinicians are well aware that emotions play an important part in most illnesses. Please ***underline*** *the reply which comes closes to how you have been feeling* ***in the past week****.*
Do not take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response.

F1. **I feel tense or 'wound up'**:
- 3 Most of the time
- 2 A lot of the time
- 1 From time to time, occasionally
- 0 Not at all

F2. **I still enjoy the things I used to enjoy**
- 0 Definitely as much
- 1 Not quite so much
- 2 Only a little
- 3 Hardly at all

F3. **I get a sort of frightened feeling as if something awful is about to happen**:
- 3 Very definitely and quite badly
- 2 Yes, but not too badly
- 1 A little, but it doesn't worry me
- 0 Not at all

F4. **I can laugh and see the funny side of things**
- 0 As much as I always could
- 1 Not quite so much now
- 2 Definitely not so much now
- 3 Not at all

F5. **Worrying thoughts go through my mind**:
- 3 A great deal of the time
- 2 A lot of the time
- 1 From time to time but not too often
- 0 Only occasionally

F6. **I feel cheerful**:
- 3 Not at all
- 2 Not often
- 1 Sometimes
- 0 Most of the time

F7. **I can sit at ease and feel relaxed**:
- 0 Definitely
- 1 Usually
- 2 Not often
- 3 Not at all

F8. **I feel as if I am slowed down**:
- 3 Nearly all the time
- 2 Very often
- 1 Sometimes
- 0 Not at all

F9. **I get a sort of frightened feeling like 'butterflies' in the stomach**:
- 3 Not at all
- 2 Occasionally
- 1 Quite often

0 Very often

F10. **I have lost interest in my appearance**:

0 Definitely
1 I don't take as much care as I should
2 I may not take quite as much care
3 I take as much care as ever

F11. **I feel restless as if I have to be on the move**:

3 Very much indeed
2 Quite a lot
1 Not very much
0 Not at all

F12. **I look forward with enjoyment to things**:

1. As much as ever I did
2. Rather less than I used to
3. Definitely less than I used to
4. Hardly at all

F13. **I get sudden feelings of panic**:

3 Very often indeed
2 Quite often
1 Not very often
0 Not at all

F14. **I can enjoy a good book, or radio, or TV programme**:

0 Often
1 Sometimes
2 Not often
3 Very seldom

Appendix (11) : Impact of Weight on Quality of Life-Lite (IWQOL-Lite)

Impact of Weight on Quality of Life Questionnaire (IWQOL-Lite)

Please place an (✓) in the box which applies best to each of the numbered statements. All of the results will be *strictly* confidential. Most of the questions directly relate to food or eating, although other types of questions have been included. Please answer each question carefully. Thank you.

1. Because of my weight, I have trouble picking up objects.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

2. Because of my weight, I have trouble tying my shoes.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

3. Because of my weight, I have difficulty getting up from chairs.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

4. Because of my weight, I have trouble using stairs.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

5. Because of my weight, I have difficulty putting on or taking off my clothing.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

6. Because of my weight, I have trouble with mobility.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

7. Because of my weight, I have trouble crossing my legs.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

8. I feel short of breath with only mild exertion.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

9. I am troubled by painful or stiff joints.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

10. My ankles and lower legs are swollen at the end of the day.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

11. I am worried about my health.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

12. Because of my weight, I am self-conscious.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

13. Because of my weight, my self-esteem is not what it could be.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

14. Because of my weight, I feel unsure about myself.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

15. Because of my weight, I don't like myself.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

16. Because of my weight, I am afraid of being rejected.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

17. Because of weight, I avoid looking in mirrors or seeing myself in photographs.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

18. Because of my weight, I am embarrassed to be seen in public places.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

19. Because of my weight I do not enjoy sexual activity.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

20. Because of my weight, I have little or no sexual desire.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

21. Because of my weight, I have difficulty with sexual performance.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

22. Because of my weight, I avoid sexual encounters whenever possible.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

23. Because of my weight, I worry about fitting into seats in public places (e.g. restaurants, cars, theatres, airplanes)

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

24. Because of my weight, I worry about fitting through aisles or turnstiles.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

25. Because of my weight, I worry about finding chairs that are strong enough to hold my weight.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

26. Because of my weight, I experience ridicule, teasing, or unwanted attention.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

27. Because of weight, I experience discrimination by others.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

28. Because of my weight, I have trouble getting things accomplished or meeting my responsibilities.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

29. Because of my weight, I am less productive than I could be.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

30. Because of my weight, I don't receive appropriate raises, promotions, or recognition at work.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

31. Because of my weight, I am afraid to go on job interviews.

❑ Always True ❑ Usually True ❑ Sometimes True ❑ Rarely True ❑ Never True

Appendix (12) : Short-Form 36 Health Survey Questionnaire (SF36)

SF-36(tm) Health Survey

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

1. In general, would you say your health is:

Excellent

Very good

Good

Fair

Poor

2. Compared to one year ago, how would you rate your health in general now?

Much better now than a year ago

Somewhat better now than a year ago

About the same as one year ago

Somewhat worse now than one year ago

Much worse now than one year ago

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

Yes, limited a lot.

Yes, limited a little.

No, not limited at all.

4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?

Yes, limited a lot.

Yes, limited a little.

No, not limited at all.

5. Lifting or carrying groceries.

Yes, limited a lot.

Yes, limited a little.

No, not limited at all.

6. Climbing several flights of stairs.

Yes, limited a lot.

Yes, limited a little.

No, not limited at all.

7. Climbing one flight of stairs.

Yes, limited a lot.

Yes, limited a little.

No, not limited at all.

8. Bending, kneeling or stooping.

Yes, limited a lot.

Yes, limited a little.

No, not limited at all

9. Walking more than one mile.

Yes, limited a lot.
Yes, limited a little.
No, not limited at all.

10. Walking several blocks.

Yes, limited a lot.
Yes, limited a little.
No, not limited at all.

11. Walking one block.

Yes, limited a lot.
Yes, limited a little.
No, not limited at all.

12. Bathing or dressing yourself.

Yes, limited a lot.
Yes, limited a little.
No, not limited at all.

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

13. Cut down the amount of time you spent on work or other activities?

Yes No

14. Accomplished less than you would l

Yes No

15. Were limited in the kind of work or
activities

Yes No

16. Had difficulty performing the work or other activities (for example, it took extra time) Yes No

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

17. Cut down the amount of time you spent on work or other activities?

Yes No

18. Accomplished less than you would like

Yes No

19. Didn't do work or other activities as carefully as usual

Yes
No

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all
Slightly
Moderately
Quite a bit
Extremely

21. How much bodily pain have you had during the past 4 weeks?

Not at all
Slightly
Moderately
Quite a bit
Extremely

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all
Slightly
Moderately
Quite a bit
Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks?

23. did you feel full of pep?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

24. have you been a very nervous person?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

25. have you felt so down in the dumps nothing could cheer you up?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

26. have you felt calm and peaceful?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

27. did you have a lot of energy?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

28. have you felt downhearted and blue?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

29. did you feel worn out?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

30. have you been a happy person?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

31. did you feel tired?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- ❑ All of the time
- ❑ Most of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

How TRUE or FALSE is each of the following statements for you?

33. I seem to get sick a little easier than other people
    - ❑ Definitely true
    - ❑ Mostly true
    - ❑ Don't know
    - ❑ Mostly false
    - ❑ Definitely false

34. I am as healthy as anybody I know
    - ❑ Definitely true
    - ❑ Mostly true
    - ❑ Don't know
    - ❑ Mostly false
    - ❑ Definitely false

35. I expect my health to get worse
    - ❑ Definitely true
    - ❑ Mostly true
    - ❑ Don't know
    - ❑ Mostly false
    - ❑ Definitely false

36. My health is excellent
    - ❑ Definitely true
    - ❑ Mostly true
    - ❑ Don't know
    - ❑ Mostly false

Appendix (13) : Alcohol Use Disorders Identification Test (AUDIT)

AUDIT					
How often do you have a drink containing alcohol?	Never	Monthly or less	2 - 4 times per month	2 - 3 times per week	4+ times per week
How many units of alcohol do you drink on a typical day when you are drinking?	1 -2	3 - 4	5 - 6	7 - 9	10+
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you or somebody else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?	No		Yes, but not in the last year		Yes, during the last year

Appendix (14) : Dietary food record

4 DAY
DIETARY RECORD

Study ID ----------

Study Visit ----------

Name: ----------
Date of Birth: ----------
Height: ----------
Weight: ----------
Date: ----------

This record is designed to obtain accurate information about the type and quantity of food that you eat.

Please complete this diary for 3 weekdays and 1 WEEKEND day.
Please answer the General Question section and then go on to the Food Record.

Please return to Haya Alessimii on your next visit.
Email: h.alessimii16@imperial.ac.uk

GENERAL QUESTIONS

Which type of bread do you **usually** eat?

- ❑ White
- ❑ Brown/Hovis
- ❑ Granary
- ❑ Wholemeal
- ❑ None

Do you **usually** buy large or small loaves, sliced or unsliced?

- ❑ Large
- ❑ Small
- ❑ Sliced
- ❑ Unsliced

If you eat any type of biscuit regularly, please specify which brands?

_____

_____

_____

Which type of milk do you **usually** use?

- ❑ Full cream milk (blue cap)
- ❑ Semi-skimmed milk (green cap)
- ❑ Skimmed milk (red cap)
- ❑ None

How much milk do you **usually** use?

- ❑ 1-2 pints daily
- ❑ ½-1 pint
- ❑ ¼-½ pint
- ❑ None

How many tablespoons of milk do you take in tea and coffee?

_____ tablespoons milk in a cup of tea

_____ tablespoons milk in coffee

_____ None.

Which kind of fat do you usually use on bread, crispbreads etc?

- ❑ Butter
- ❑ Margarine
- ❑ Low fat spread

Which brand do you usually use? _____

What do you do with the visible fat on your meat?

- ❑ Eat most of the fat
- ❑ Eat as little as possible
- ❑ Eat some of the fat
- ❑ Don't eat meat

How often do you eat food that is fried?

- ❑ Daily
- ❑ 1-3 times/week
- ❑ 4-6 times/week
- ❑ Less than once/week

Do you drink alcoholic drinks?

❑ YES ❑ NO

If the answer is **Yes**, please indicate how many units you drink per week?

1 unit = ½ pint beer/lager
1 glass wine,
1 tot spirit.

_____ units per week.

Who tends to do the shopping and cooking?

_____

FOOD RECORD

Read through these instructions and the example carefully once or twice before you start.

We would like you to record, as accurately as possible, what you eat and drink for 4 days.

Please record **ALL** food and drink consumed. Record at the time of eating and **NOT** from memory at the end of the day. Keep this record sheet with you throughout the day.

You should include all meals and snacks, plus sweets, drinks etc. When recording food eaten at meals, please include any sauces, dressing or extras eg: gravy, salad dressing, pickles, as well as the main food.

If you do not eat a particular meal or snack, simply draw a line across the page at this point.

Guidelines for describing food & drink:

1. Please give details of method of cooking eg: grilled, boiled, roasted.

2. Give as many details as possible about the type of food you eat:

   a) State brand name where applicable

      e.g.: Prince's sardines in tomato sauce OR
      Sainsburys half-fat Edam cheese.

   b) Name the type of biscuit, cake or cereal

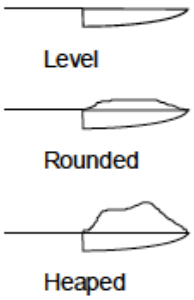
      e.g.: Rich Tea, Madeira, Bran flakes.

   c) Name the type of cheese, fish or meat

      e.g.: Cheshire cheese, haddock fillet, pork chop.

3. Suggestions for recording quantity of food and drink:

a) For many foods such as vegetables, cereals and some fruit a household measure is adequate, state the number of teaspoons (tsp) or tablespoons (tbsp) or cups, and whether level, rounded or heaped.



b) All convenience foods have their weight on the packaging, and this can be quoted

e.g.: 150g carton Ski raspberry yoghurt OR
½ 15 oz can baked beans.

c) Bread, fruit loaves etc. Indicate the size of the loaf and the thickness of the slice

e.g.: 1 thick slice granary bread, small loaf.

d) Cheese, fish, meat. When possible, please weigh your portions of these foods. Otherwise describe as well as you can.

e.g.: 2 large thin slices ham OR
2 small lamb chops (no fat eaten) OR
Medium fillet of cod grilled with 1 tsp flora OR
Cube of cheddar cheese the size of a matchbox.

4.Write down where you are and who you are with when eating and drinking.

5. Rate your hunger before you eat using the hunger scale below.
6. Record your mood/feelings and/or any symptoms and the time they occur

Hunger scale:

1	2	3	4	5	6	7	8	9	10
Physically Faint	Ravenous	Fairly Hungry	Slightly Hungry	Neutral	Pleasantly satisfied	Full	Stuffed	Bloated	Nauseous

Remember to include everything you eat and drink including snacks and nibbles.

Please do not change what you normally eat just because you are filling in this record - Be Honest!

Look at the example of how to fill in you record - you may find this helpful.

THANK YOU VERY MUCH FOR YOUR HELP

DIETARY RECORD SHEET - EXAMPLE

Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.
Record method of cooking, type and quantity of food
eg: 6 tbsp boiled wholemeal spaghetti, 2 egg sized roast potatoes.
DAY: Example DATE: 1st June 1995

MEAL/ SNACK	QUANTITY EATEN	DETAILS OF FOOD & DRINK	Feelings
Early Morning:	1 cup 1 tbsp	Tea with Skimmed milk	Hunger
Breakfast:	3 heaped tbsp ¼ pint 1 medium slice 1 tsp 2 mugs	Branflakes (Kellogg's) Skimmed milk for cereal & drinks Wholemeal bread (large loaf) Flora extra light margarine Coffee	Hunger
During Morning:	1 mug 1 tbsp 1 medium	Coffee with skimmed milk Apple (eaten with skin)	Hunger
Midday:	4 slices 4 level tsp 2 thin slices 1 large 1 large 1 can (330ml)	Sandwiches: wholemeal bread (Allinson's) large loaf, sliced Flora extra light margarine Ham (no fat) Tomato Banana Diet Tango	Hunger

Example DATE: 1st June 1995

MEAL/ SNACK	QUANTITY EATEN	DETAILS OF FOOD & DRINK	Feelings
During Afternoon:	1 glass 25g pkt	Low Calorie squash made with concentrated squash KP roasted salted peanuts	Hunger
Evening Meal:	4 heaped tbsp 1 apple sized 3 tbsp 1 x 150g tub 1 glass 1 cup 1 tbsp	Chicken & mushroom casserole (home-made with skimmed milk in the sauce) Jacket potato Broccoli, boiled Shape raspberry yoghurt Half mineral water/half natural orange juice Tea with skimmed milk	Hunger
During Evening:			Hunger
Bedtime Snack:	1 mug 1 tsp ½ mug 2	Ovaltine made with: Ovaltine ordinary silver top milk, the rest water Rich Tea biscuits (Sainsburys).	Hunger

Appendix (15) : Cup arrangements and scoring Sheets for Sweet Taste Detection test

At baseline visit before GOP:

Please put √ where the solution is correctly identified and X where it was not Identified

B1	1 S6	2 S1	3 W	4 S5	5 W	6 S3	7 W	8 S4	9 W	10 S2	11 W	12 W	13 S7	14 W
B2	15 S6	16 W	17 W	18 S4	19 W	20 S3	21 W	22 S7	23 W	24 S5	25 S1	26 W	27 S2	28 W
B3	29 W	30 S7	31 W	32 W	33 S2	34 S5	35 S6	36 W	37 S4	38 W	39 W	40 S3	41 S1	42 W
B4	43 S3	44 W	45 S2	46 S6	47 W	48 W	49 S7	50 W	51 W	52 W	53 S1	54 W	55 S4	56 S5
B5	57 W	58 S3	59 S2	60 W	61 S1	62 S7	63 W	64 S5	65 S6	66 W	67 S4	68 W	69 W	70 W
B6	71 W	72 S6	73 W	74 S5	75 W	76 S4	77 S1	78 W	79 W	80 W	81 S7	82 W	83 S3	84 S2
B7	85 W	86 S5	87 W	88 W	89 S2	90 W	91 S3	92 W	93 S6	94 S1	95 W	96 S4	97 W	98 S7
B8	99 S1	100 S6	101 W	102 S5	103 S7	104 W	105 W	106 W	107 W	108 S2	109 S3	110 W	111 S4	112 W

Con. Cup arrangements and scoring Sheets for Sweet Taste Detection test

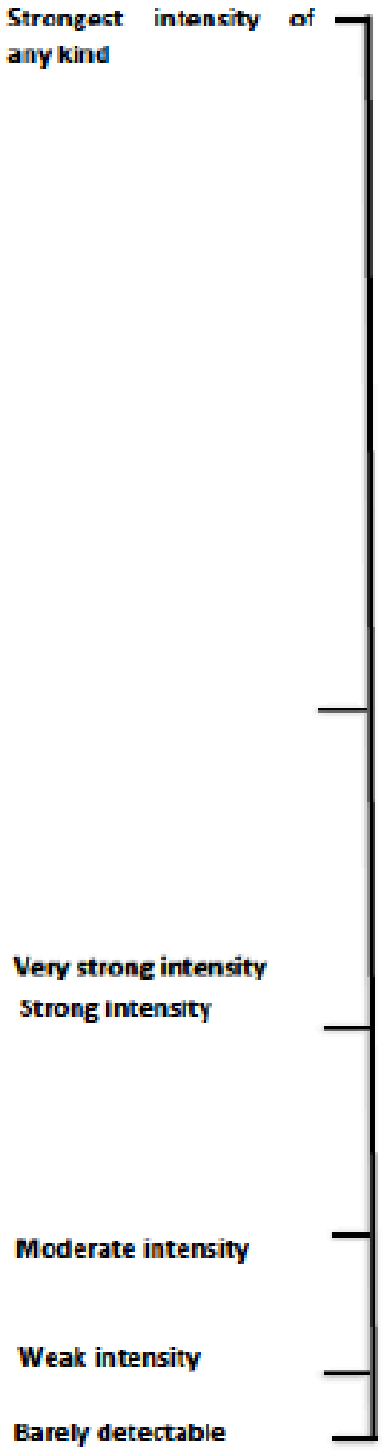
At one-month of GOP:

Please put √ where the solution is correctly identified and X where it was not Identified

B1	1 W	2 S6	3 W	4 W	5 W	6 S7	7 S2	8 W	9 S5	10 S1	11 S3	12 W	13 S4	14 W
B2	15 W	16 S5	17 S3	18 S6	19 S2	20 W	21 S7	22 S1	23 W	24 W	25 W	26 W	27 S4	28 W
B3	29 S6	30 S2	31 W	32 W	33 W	34 S1	35 W	36 S5	37 W	38 S4	39 W	40 S3	41 W	42 S7
B4	43 W	44 S7	45 W	46 S1	47 S5	48 W	49 S3	50 S6	51 W	52 W	53 S2	54 W	55 S4	56 W
B5	57 W	58 W	59 S1	60 S2	61 S3	62 W	63 S6	64 W	65 W	66 S4	67 W	68 S7	69 S5	70 W
B6	71 W	72 S3	73 S1	74 W	75 S4	76 W	77 S7	78 S6	79 W	80 W	81 W	82 S2	83 S5	84 W
B7	85 S7	86 W	87 S4	88 W	89 S2	90 W	91 S6	92 W	93 S3	94 W	95 S1	96 W	97 S5	98 W
B8	99 S2	100 W	101 S4	102 W	103 S5	104 W	105 W	106 W	107 W	108 S7	109 S6	110 S3	111 S1	112 W

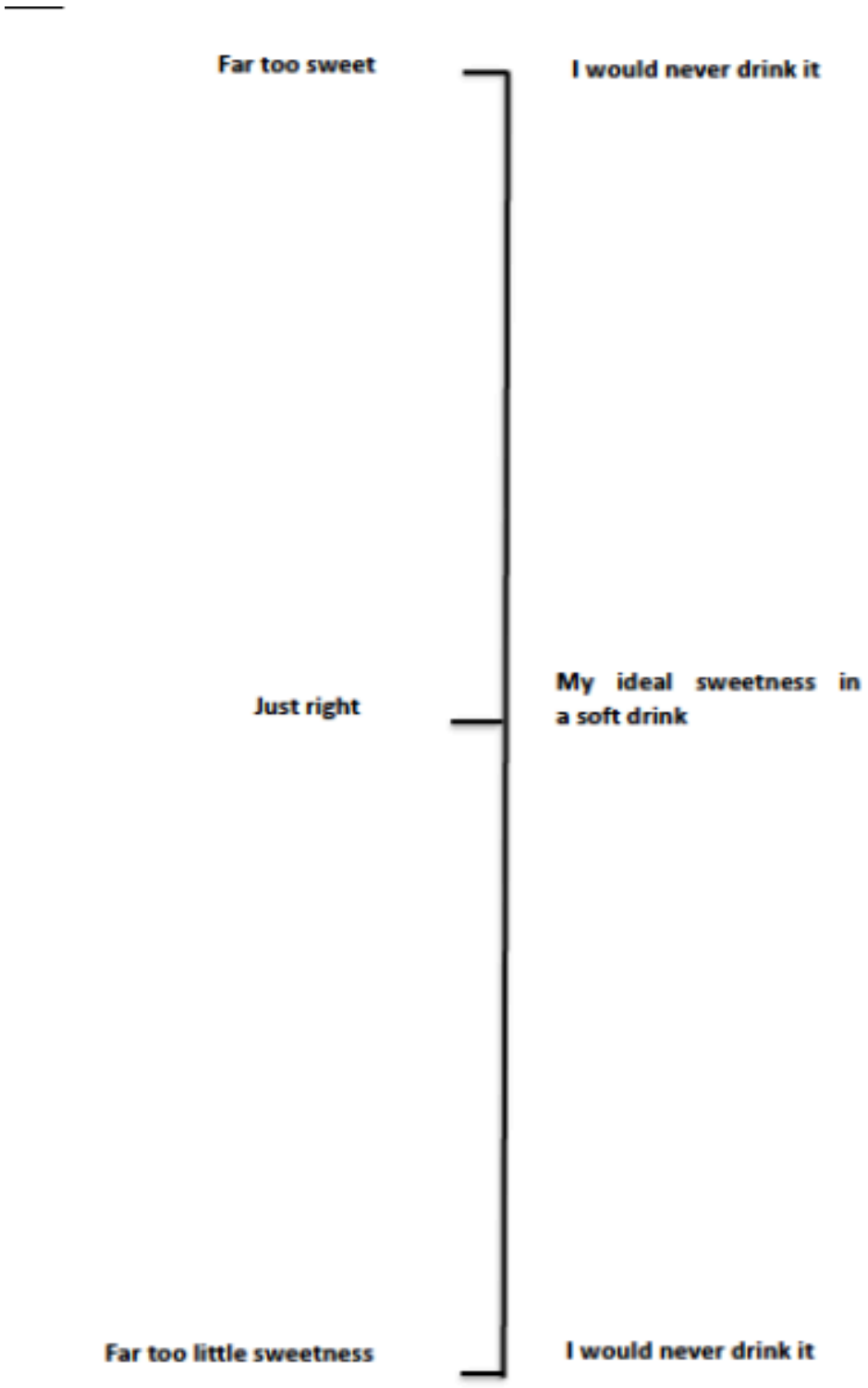
Appendix (16) : The Intensity generalised labelled magnitude scale (gLMS)

On the scale below, please indicate, using a horizontal mark, the INTENSITY of the sweet taste relative to sensations you have ever experienced of any kind, not just taste (e.g., sight, sound).



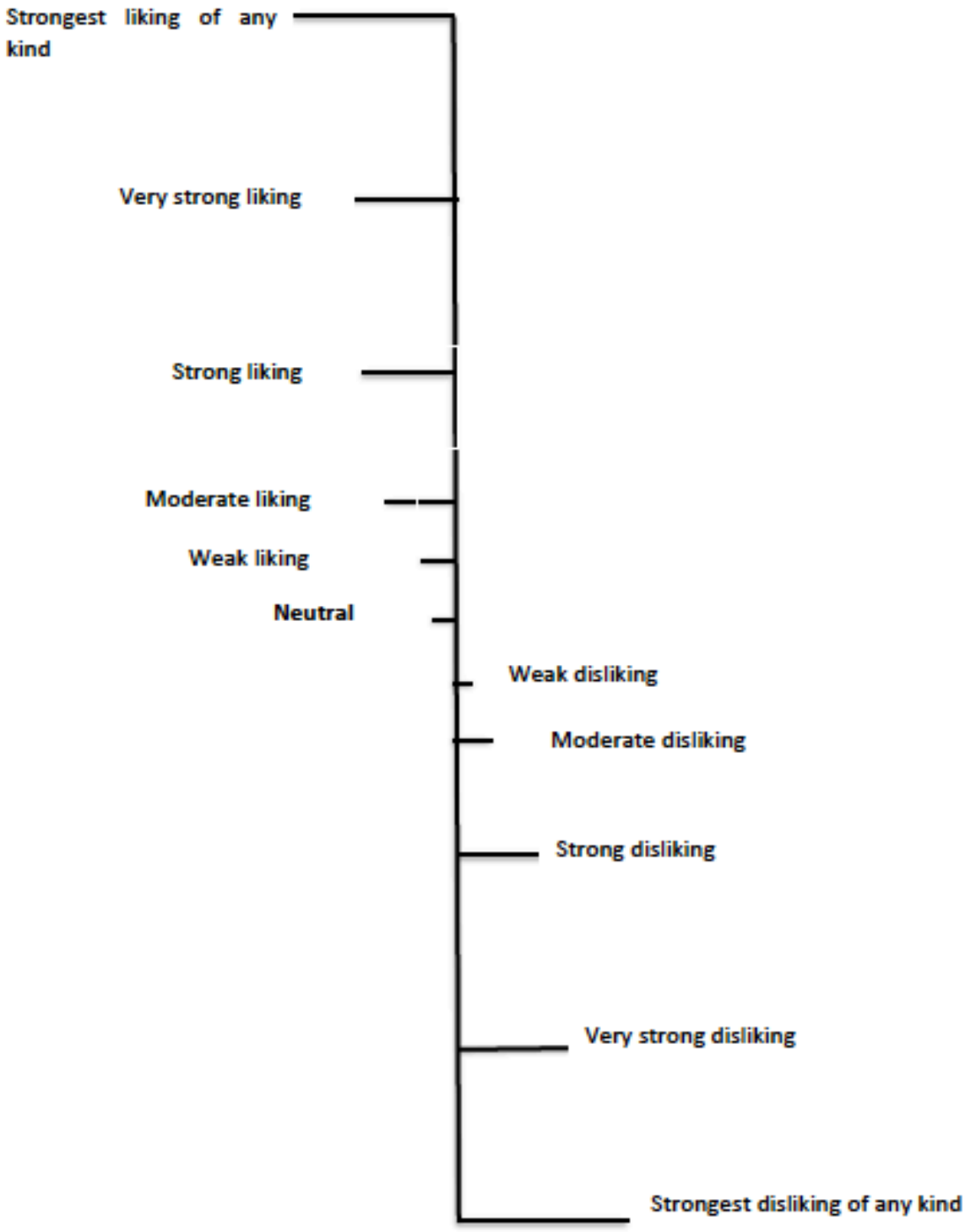
Appendix (17) : The Consummatory Taste Reward Scales

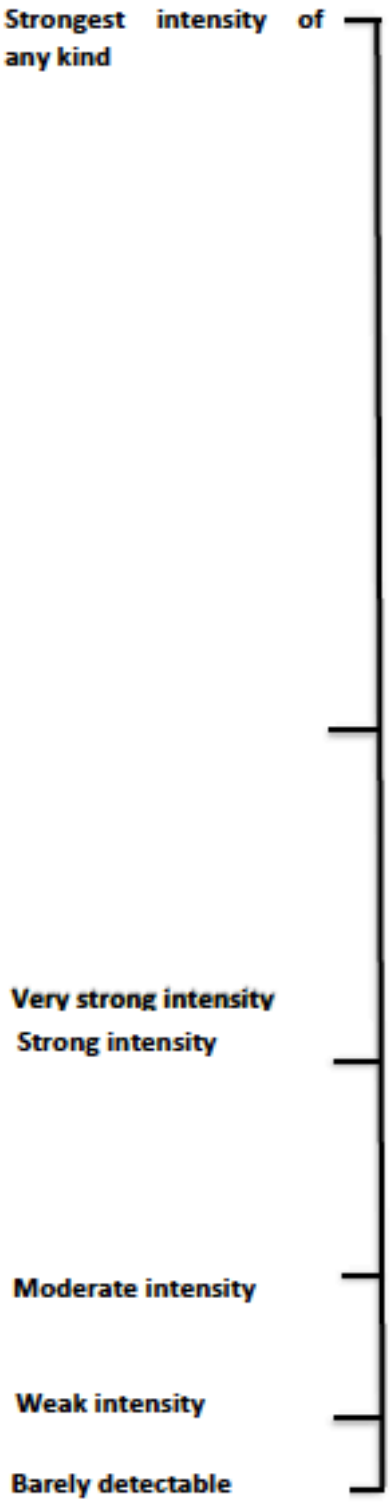
Just About Right (JAR) scale on the scale below, please indicate, using a horizontal mark, how close the SWEETNESS of the solution you have just tasted is to your ideal sweetness in a soft drink.



Appendix (18) : gLMS Hedonic scale

On the scale below, please indicate, using a horizontal mark, how much you LIKE the drink you have just tasted relative to any "liking" you have ever experienced of any kind (i.e., of any sensation).



Appendix (19) : Intensity Scale

On the scale below, please indicate, using a horizontal mark, the INTENSITY of the sweet taste relative to sensations you have ever experienced of any kind, not just taste (e.g., sight, sound).