

Changes in eating behaviour and meal patterns following Vertical Sleeve Gastrectomy

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ABSTRACT

Anecdotal evidence from clinical observations and evidence in rodents after vertical sleeve gastrectomy (VSG) suggest a shift in food preferences. Direct measures of behaviour to study the effects of VSG on the food preferences are unknown. This study aimed to investigate (1) Changes in eating behaviour and meal patterns after VSG, (2) Changes in sweet taste detection thresholds after VSG, (3) Changes in appetitive behaviour as a marker of changes in reward after VSG, and (4) Changes in consummatory behaviour as a marker of changes in reward after VSG in adolescents' subjects.

The project recruited 50 adolescents after VSG and 35 as controls. The ages were 15 ± 0.27 and 14 ± 0.28 for the subjects after VSG and controls respectively. 42 % of the subjects were females and 58 % males, with the mean BMI of (51.1 ± 1.0) for VSG and (31.9 ± 1.1) for control subject. The parameters recorded for each aim included; Aim 1: Meal duration, meal size, pre-meal hunger and post-meal satiation that were assessed before and after VSG. Attitudes to foods, 24h recall method and FFQ were measured. Aim 2: The intensity of sweet taste stimuli assessed before and after VSG, using the constant stimuli methods. Aim 3: The appetitive reward of fat and sweet taste stimuli was assessed before and after VSG, using the Progressive Ratio Task. Aim 4: The consummatory reward of fat and sweet taste stimuli was assessed before and after VSG, using taste reactivity by recording and analysing facial expressions to determine the ingestive behaviour in response to stimulants.

The results demonstrated; Aim 1: Changes in food preferences towards healthier choices, eating behaviour and meal pattern after VSG (all $p < 0.05$). Aim 2: No changes in sucrose detection threshold after VSG ($p = 0.6$). Aim 3: Appetitive reward value as measured by the breakpoint of the tastant decreased after VSG ($p = 0.02$). Aim 4: Consummatory reward value of the tastant as measured by behaviours associated with positive ingestive behaviours decreased after VSG as well ($p = 0.03$).

In conclusion obese adolescents after VSG have a shift in food preferences to healthier food choices, as well as eating behaviour and meal patterns. VSG changed the Hedonic value of high fat and sugary food as suggested by changes in Appetitive and Consummatory behaviour in response. However VSG had no effect on the sensory domain as regards sweet sensitivity. Taken together VSG may improve the quality of food selected after surgery by reducing the reward value of high fat and sugary foods.

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FREQUENTLY USED ABBREVIATIONS

%	Percentage
°C	Celsius Temperature Scale
AGB	Adjustable Gastric Banding
ANOVA	Analyses Of Variance
ASMBS	American Society for Bariatric and Metabolic Surgery
AUs	Action Unit system
BD	Biliopancreatic Diversion
BMI	Body Mass Index
BMOD	Behaviour Modification
BMR	Basal Metabolic Rate
BPD/DS	Biliopancreatic Diversion– Duodenal Switch
BPL	Biliopancreatic Limb
BT	Behavioural Techniques
C	Concentration
CAD	Coronary Artery Disease
cAMP	cyclic Adenosine Mono Phosphate
Carb	Carbohydrates
CB1	CannaBinoid receptor type 1
CBT	Cognitive Behaviour Therapy
CDC	Centers for Disease Control and Prevention
CHD	Coronary Heart Disease
CHO	Cholesterol
cm	Centimetre
CR	Cognitive Restraint
CRC	Clinical Research Centre
DED	Dietary Energy Density
DS	Duodenal Switch
EC50s	Half Maximal Effective Concentration
ED	Dietary Energy Density
EE	Energy Expenditure
EE	Emotional Eating
EI	Energy Intake
EMA	European Medicines Agency
EMG	Electromyogram Measurements
Eq	Equation
EWL	Excess Weight Loss
FA	False Alarm
FACS	Facial Action Coding System
FDA	Food and Drug Administration
FFQ	Food Frequency Questionnaire
FGF	Fibroblast Growth Factor
FGFR4	Fibroblast Growth Factor Receptor
FGRR1c	Fibroblast Growth Factor Receptor c-kit
fMRI	Functional MRI
FW	Food Weight
FXR	Farnesoid X Receptor
g	Grams
g/min	Grams/Minutes
GB	General Behaviour

GERD	Gastroesophageal Reflux Disease
GI	glycemic index
gLMS	general Labeled Magnitude Scale
GLP-1	Glucagon-Like Peptide-1
HCl	Hydrochloride
HDL	High Density Lipo Protein
HGI	High Glycemic Index
INR	International Normalized Ratio
JIB	Jejunum-Ileal Bypass
JJ	Jejunum-Jejunal
Kcal	Calories
Kg	Kilo Grams
kg/m ²	Kilo Grams/Meters square
KKUH	King Khalid University Hospital
KSA	Kingdom of Saudi Arabia
KSU	King Saud University
LC	Low-Carbohydrate
LCDs	Low Calorie Diets
LCKD	Low Carbohydrate Ketogenic Diet
LDS	Laparoscopic Duodenal Switch
LEARN	Lifestyle, Exercise, Attitudes, Relationship, and Nutrition
LFD	Low-Fat Diet
LGI	Low Glycemic Index
LRSG	Laparoscopic Re-Sleeve Gastrectomy
m	Minutes
M&Ms	Crispy Candies, Mars UK Limited, Slough UK
ml	milliLitres
mL/min	milliLitres/Minutes
mM	millimolar
MYSTAT	Statistics and Statistical Graphics Software
N	Number
N/A	Not Available
NEV	Negative Effective Values
NS	Not Significant
O	Orlistat
OFC	Orbito Frontal Cortex
p	p Value
P(hit)	Corrected Hit Rate
PEV	Positive Effective Values
POST-OP	Post – Operation
PRT	Progressive-Ratio Task
PRE-OP	Pre – Operation
PRISM	Graph Pad Prism Statistics Guide
PYY	Peptide YY
QoL	Quality of Life
RCT	Randomized Controlled Trial
REE	Reduced resting Energy Expenditure
RMR	Resting Metabolic Rate
RYGB	Proximal Roux-en-Y gastric bypass
SA	Saudi Arabia

SCOUT	Sibutramine Cardiovascular Outcome Trial
SD	Standard Deviation
SEM	Standard Error of the Mean
SG	Sleeve Gastrectomies
SOS	Swedish Obesity Subjects Study
SPSS	Statistical Analysis Software
SR	Sustained Release
T2DM	Type 2 Diabetes Mellitus
TFEQ-21	Three-Factor Eating Questionnaire
TGR5	G Protein-Coupled Receptors
UE	Uncontrolled Eating
UK	United Kingdom
US	United States
VAS	Visual Analogue Scales
VSG	Vertical Restrictive (sleeve) Gastrectomy
WHO	World Health Organization
XENDOS	Xenical in the Prevention of Diabetes in Obese Subjects
X-PERT	Health Structured Education Programme

CHAPTER 1

INTRODUCTION

1.1 Introduction

Body fat is mainly composed of adipose tissue in the form of triglycerides, and its measurement is a major challenge to researchers and clinicians. Fat is mainly stored in subcutaneous tissue and intra-abdominal structures, and a substantial amount of fat can also exist in muscles, particularly in the elderly (1). The term obesity is often used to refer to an excess of body fat, which usually accounts for up to 25% of body weight in women and 18% in men (2). A number of methods can be used to quantify the proportion of fat in our body, but due to its low cost and simplicity, obesity is now defined in relation to the calculated body mass index [BMI = weight in kilograms divided by the height in meters squared (kg/m^2)] (3). BMI has replaced the more traditional measure of percentage excess weight, or the proportion by which an individual's weight exceeds the weight considered ideal for gender and age (4). Overweight and obesity are defined in adults using BMI cut-offs of ≥ 25 and $\geq 30 \text{ kg}/\text{m}^2$, respectively. According to the Centres for Disease Control and Prevention (CDC) definitions, children and adolescents with a BMI ≥ 85 th and ≥ 95 th percentiles are considered overweight, and obese, respectively (5;6). Obesity is a multifactorial disease, which results from an interaction between the genetic tendency of a person and numerous environmental factors including diet and lifestyle. Several studies have attempted to determine the relative contributions of genetic and environmental factors in the aetiology of obesity. Genetic factors have been suggested to contribute 70%, and environmental factors 30% (7). However, what is much more certain is the interaction between the environment and genetics (7). Genes may also contribute to the differences between individuals in resting metabolic rate (RMR), weight gain in response to overfeeding, and body fat distribution (8-10). RMR, as the largest component of daily energy expenditure, has been shown to have a strong genetic component (9;11). However, the influence of a low RMR on the aetiology of obesity remains controversial. Stunkard et al. found that the genotype of some individuals who are genetically prone to developing obesity, might be expressed only under certain adverse environmental conditions, such as exposure to, and consumption of, high-fat diets, and

engaging in sedentary lifestyles (7). Risk factors for obesity also include social factors, parental obesity, high birth weight, early maturation, and other behavioural and psychological factors (12). Portion size might be another reason for increased consumption and hence greater energy intake (13;14). The mechanisms preventing an obese person from losing weight and maintaining weight loss have only been partly elucidated (15).

1.2 Obesity Epidemiology

Obesity is considered the “disease of the 21st century”, and results in physical and psychological co-morbidities, as well as poor quality of life (QoL) (16). The global prevalence of obesity has increased dramatically over the last three decades, among adults and children, across urban and rural areas, and within both developing and developed countries. Over 400 million people are presently diagnosed as obese (BMI ≥ 30 kg/m²) and almost 1.6 billion are overweight (BMI 25-29.9 kg/m²) (17).

1.2.1 Adult obesity worldwide

Linear regression models have been employed to explain the average annual increase and future projections for prevalence. Worldwide, the proportion of adults with overweight (BMI ≥ 25 kg/m²) increased between 1980 and 2013 from 28.8% to 36.9% in men and from 29.8% to 38.0% in women (18). The prevalence of obesity in adults has increased from 13% to 32% between the 1960s and 2004. Presently, 66% of adults are considered overweight or obese (5). In some developed countries, the estimated prevalence of obesity among adults exceeds 50%, although the increase has slowed since 2006 (18). Annual increases in prevalence have ranged from 0.3 to 0.9%. The prevalence of obesity has been predicted to reach 44.2% by 2020 (19), with a predicted 41% of adults obese and 75% overweight or obese by 2030 (5), with a linear increase thereafter. Trends also suggest 65 million more obese adults in the USA and 11 million more obese adults in the UK by 2030

(20). About one-third of the people in the United States (US) are currently classified as obese (18;21;22). Similarly, more than 25% and 50% of adults in the UK are respectively considered obese and overweight (18). The prevalence of obesity and overweight between US children and adults has more than doubled since the 1970s, and the rate continues to rise (5). Between 1960 and 1980 the prevalence of obesity was relatively stable, after which it began to increase again, more than doubling from 15% in 1980 to 34% in 2006 (Figure 1.2.3-1) (3;23). Despite this, the prevalence of obesity in this age group remains higher in the US than most European Countries (18;24). Excess weight has also increased considerably in children and adolescents within developed countries; an estimated 23·8% of boys and 22·6% of girls were overweight or obese in 2013. Increases have been observed among children and adolescents in developing countries in 2013, from 8·1% to 12·9% for boys and from 8·4% to 13·4% in girls (18). The Middle Eastern countries of Egypt, Libya, Iran, Turkey, and gulf region countries, such as Saudi Arabia (SA), now have some of the highest prevalences of obesity in adults and young people (18;25;26), which may in part be explained in SA by cultural views, customs and traditions of internal marriages.

1.2.2 Child obesity worldwide

Over the past century, a large proportion of the nutrition research and policy relating to the developing world, focused on undernutrition and poverty-related problems. More recently there is growing concern regarding worrying overweight and obesity trends in these societies (27). Defined as a BMI at or above the 99th percentile, childhood obesity is one of the most serious public health and medical problems in the US, Europe, Middle East and the Gulf area. Worldwide, over 22 million children under the age of 5 years are overweight, as are 155 million children of school age. Overweight prevalence in Africa and Asia is below 10%, while in the Americas and Europe it is above 20% (28). Other estimates suggest that 16% of children and adolescents are overweight and 34% are at risk of becoming overweight (5). It is of great importance to understand the trends in childhood obesity because of the many adverse effects on health it can impose, both during childhood and

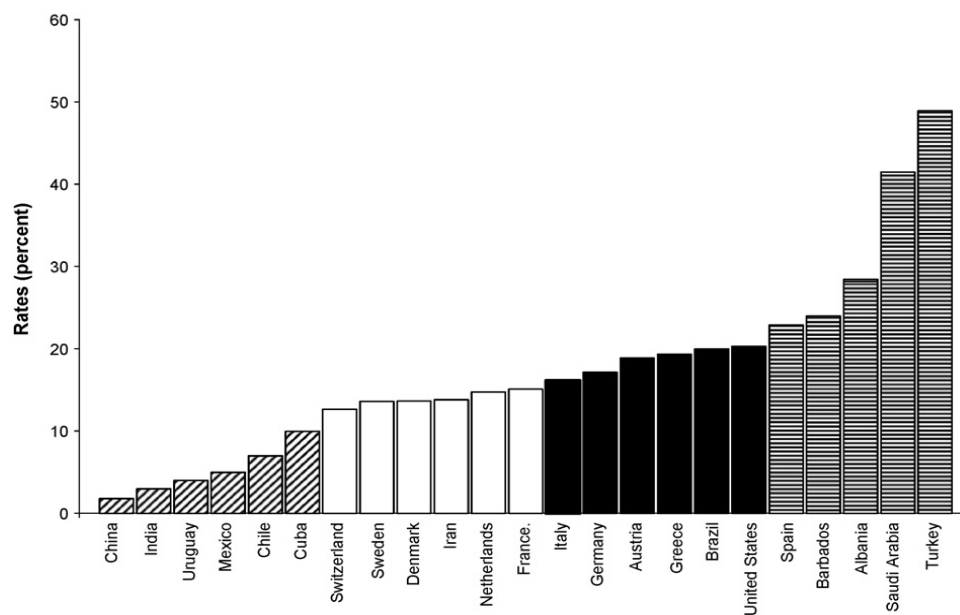
through adulthood (29). Wang has presented a unique comparative study examining data from 4 countries and representing approximately one-third of the global population. This study shows the trends in childhood and adolescent underweight and overweight status (30). The prevalence of overweight increased in 3 of the 4 countries between the survey periods of each country (1971-1999), tripling in Brazil, almost doubling in the US, and increasing by a fifth in China. On the contrary, the prevalence of overweight in Russia was reported to have decreased from 15.6% to 9.0%. This was during a period of great economic stress and a marked reduction in the energy density of the typical diet (27;31). Europe's obesity estimates vary from 3-21% depending on how obesity is defined (32), with an estimated 10-17% in England (33;34). Some suggest that the prevalence of childhood obesity has already tripled across the past 30 years in the US, and the health implications and related medical costs of the disease are marked (35). Annual hospital-related costs linked to treating obese young people have increased from 35 million US dollars (USD) in 1979 to more than 127 million USD in 1997-1999, based on the 2001 USD value (36).

1.2.3 Obesity in the Middle East - Saudi Arabia

The rapid socio-cultural changes that have occurred in the Arabian Gulf region, since the discovery of oil reserves and the economic boom during the 1970s and 1980s, have resulted in a rapid and alarming increase in obesity (37;38). Among the factors contributing to obesity in SA, is significant change to dietary behaviours, in terms of quantity and quality, both of which have become more "Westernised" (39). Recent studies have revealed that consumption of animal products and refined foods have increased, at the expense of fruit and vegetables (40;41). El-Bayoumy et al. suggested that the Gulf region prevalence of overweight and obesity ranges from 18% to 30 % and 15% to 19%, respectively, among children and adolescents (42;43). SA covers around two thirds of the Arabian Peninsula and has a population of 30.8 million people, of which 20.7 million are Saudis (44). According to a 2007 survey, 37% of the population are ≤ 15 years (45). Between 1995 and 2000, Al Nozha and his research group conducted a 5-year National Epidemiological Health Survey to study

Coronary Artery Disease (CAD) and its risk factors. 20,000 Saudis between men and women aged 30-70 years in rural and urban areas of the Kingdom were studied. The data showed an overall obesity prevalence of 35.6% and an additional overweight prevalence of 36.9%, suggesting that a total of 72.5% Saudis are either overweight or obese (18;46).

Figure 1.2.3-1 Prevalence of obesity across selected countries grouped in quartiles (2009) (47).



An alarmingly high obesity rate was noted in both Saudi Arabia and Kuwait. The prevalence of obesity is considered to be extremely high among Kuwaiti and Saudi pre-school children (8-9%), and Kuwait's prevalences of overweight and obesity in adolescents were among the highest in the world at 40-46% (48). In studies conducted in different regions of SA, examining children and adolescents ≤ 20 years old across both genders, 10.7-23.0% were overweight, 3.4-24.5% were considered obese, and approximately 28% in total were considered either overweight or obese (Appendix 1) (49). More than 50% of children in SA between ages 14 and 18 years had weight above the 85th percentile (49).

Among young people in Saudi Arabia, overweight and obesity were estimated to be around 27.5% among boys (11.7% overweight and 15.8% obese) between 6 and 18 years of age in 1996 (18;50), 28.0% among girls between 12 and 19 years in 1999 (51) and 37.4% for girls ≤ 20 years in 2013 (18). El Mouzan et al. used the 2005 Saudi reference dataset to calculate the BMI of children aged 5 to 18 years (52). Using the 2007 WHO definitions, the prevalence of overweight, obesity and severe obesity were defined as the proportion of children with a BMI standard deviation score more than +1, +2 and +3, respectively (53). The 2000 CDC definitions were used as a comparison (54). Their target population comprised 19,317 healthy young people between 5 to 18 years of age, 50.8% of whom were boys. The overall prevalence of overweight, obesity and severe obesity in all age groups was 23.1%, 9.3% and 2%, respectively. A significantly lower prevalence of overweight (23.8 vs. 20.4; $p < 0.001$) and obesity (9.5 vs. 5.7; $p < 0.001$) was observed when the CDC reference was used (55). In another study, carried by Al-Hazaa, between 1988 and 2005, examined school boys between the age of 6 and 14 years old, and showed that during these 17 years the mean BMI increased from 16.5 to 18 kg/m², and fat percentage increased from 13.2 to 19.7%, indicating a rising trend toward overweight and obesity among school aged children (56). Upward trends in the prevalence of non-communicable diseases may impact negatively upon individuals, health systems, social systems and public economies. The timeframe within which this impact is observed may be relatively rapid in countries with comparatively young populations (57). The occurrence of obesity in young people represents a major concern, since obesity at this age represents a frustrating and difficult disease to treat. However, it is suggested that treatment of obesity in young people should start at an early age (58). Those below 20 years of age represent the majority of the Saudi population and should be targeted with extensive efforts prevent obesity later in life (45;59).

1.2.4 Risk Factors for Obesity

Chronic risk factors

Obesity is associated with an increased risk of death. In a prospective cohort of more than 500,000

US men and women, across 10 years of follow up, Adams et al. estimated the mortality risk of death to increase by 20% to 40% in overweight patients and as much as 200% to 300% in obese patients, compared with those who are normal-weight with no smoking history (60). Obesity is also associated with increased risk for many chronic diseases, including type 2 diabetes mellitus (T2DM), hypertension, heart disease, and stroke (61). In addition, obesity is linked to numerous digestive diseases, including gastro-oesophageal reflux disease (GORD) and its complications (e.g. erosive oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma), colorectal polyps and cancer, liver disease (e.g. non-alcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma) (62). Childhood obesity has been considered a major public health problem because an obese child will usually carry their obesity into adulthood, along with the attendant increased risks of morbidity and mortality (63-67), independently of adult BMI (65;68). Specific concern surrounds of its association with risk factors for disease and diseases themselves, such as hypertension, dyslipidaemia, chronic inflammation, hyperinsulinaemia, and orthopaedic problems (69-73), as well as considerable psychosocial consequences. Obese children are usually stereotyped as unhealthy, academically unsuccessful, socially incompetent, and even lazy (74). In addition, low self-esteem and behavioural problems are commonly associated with obesity (75) .

1.3 Cost

The obesity epidemic places a major financial burden on the economy worldwide. The US Department of Health and Human Services has estimated the total economic cost of overweight and obesity in the United States to be close to \$117 billion dollars between 1995-2001(76). Furthermore, because of the increasing prevalence of overweight and obesity since 1995, the costs today are likely to be significantly higher than earlier estimates (77). According to analyses by Wang et al., based on nationally representative data collected over the past three decades, an alarming picture emerges of the ongoing obesity epidemic and related challenges for the future in terms of increasing rates and increasing health cost. Their forecasts predict that within

15 years, 80% of all adults in the US will be overweight or obese, based on current trends. Moreover, the direct health-care costs attributable to obesity and overweight will double every decade to reach an expected health care expenditure of between 860.7 and 956.9 billion US dollars by 2030 (19). What these data fail to state is the fact that every person, not just the obese, will be affected by this epidemic (78;79). Increased health care costs (80;81) will affect not only the health care industry, but also other economic sectors that have no direct relationship to health care (82).

1.4 Obesity Treatment

1.4.1 Non-Surgical treatment

Optimal strategies and policies to address the obesity epidemic have not yet been established (83). Diet and exercise are examples of strategies for obesity treatment, and considered useful for losing weight in moderately obese adults. However, it appears that, even among those individuals who successfully lose weight with these methods, most are unable to maintain the loss for long periods (84). Unfortunately, there are no acknowledged rules to guide interventions endorsing behaviour and lifestyle changes for an effective and permanent weight loss (83).

1.4.1.1 Diet induced weight loss

It is commonly believed that weight loss achieved at a slow rate is better preserved than if the weight is lost faster. However, the literature contradicts this, showing that early weight loss long-term weight maintenance (85). Several studies have shown that a greater initial weight loss, which is usually achieved in the first 2–4 weeks of treatment, is associated with a better long-term outcome (86;87). The importance of the dietary composition in the prevention and management of obesity is debated. Some have found that ad libitum consumption of low-fat diets results in short-term weight loss (88), and that a low-carbohydrate, high-protein, and high-fat diets (e.g. the Atkins diet) may result in considerable weight loss, as compared with that achieved through other types of diet (89).

Progressive weight loss rarely continues beyond 1 year (90), and weight regain in general will be unnoticed in short-term studies because it occurs rather more slowly than weight loss in over 80% of individuals who lose weight through various weight loss programs (91). About two thirds of lost weight will be regained within 1 year among those who lose weight through dietary restriction and behavioural modification, and almost all of the lost weight will be regained by the end of 5 years (92). No medical condition has produced as many potential therapeutic approaches as obesity (Appendix 2)(93). All diets have their respective proponents and followers, but solid data on the efficacy of specific diets are almost unanimously lacking. Sacks et al. have reported the results of a large, long-term trial that tested the efficacy of weight-loss diets that were high or low in carbohydrates, protein, or fat. Twenty years ago, high carbohydrate, low-fat diets became very popular, based upon the belief that calories from carbohydrates were less fattening than the same number of calories from fat. Subsequently, a high-fat, low-carbohydrate diet was promoted by Dr. Robert Atkins in the 1970s, which also enjoyed a recent revival. The appeal of high-protein diets is that protein is thought to offer more satiation per calorie than fat or carbohydrates (94). From an epidemiologic perspective, a positive health benefit has been reported to occur when protein intake is high (95). Clinical intervention studies have established evidence that an *ad libitum* high-protein diet from a variety of food sources in free-living overweight persons increases the amount of weight lost in a 6 month weight-loss programme (by 3.8 kg) by increasing satiety compared with a high-carbohydrate diet (96). Furthermore, weight-loss studies in overweight women have revealed that a high ratio of protein to carbohydrate has positive effects on markers of disease risk, including body composition, blood lipids, and glucose homeostasis. Protein's effects of increased satiety and lower glycaemic load, due to a lesser carbohydrate intake, may be responsible for these benefits (97). In a study comparing two contrasting diets, participants were assigned to a high-protein, low glycaemic index diet or a low-protein, high glycaemic index diet, with no restriction on energy intake. Compliance with the diet was better among participants following the high-protein diet, as was maintenance of weight loss. In addition, participants who followed the high-protein, low glycaemic

index diet continued to lose weight after the initial weight loss period. The higher protein content was attained by reducing the carbohydrate content, which supports the notion that reducing the glycaemic load (defined as carbohydrate content multiplied by glycaemic index) is essential for controlling body weight in obese people (96;98). Weight regain in the study was comparatively low (0.56 kg), and the general weight loss in all participants who completed the intervention was, consequently, fairly high (10.6 kg), compared with the total weight loss in most studies of similar length. As a result, researchers have concluded that because of the high rate of completion and weight maintenance in most subjects, the studied high-protein, low glycaemic index diet appears to be preferable for the prevention of weight regain (99). Considering the growing prevalence of obesity in young people, assessments of novel therapeutic interventions are necessary. For example, very low-carbohydrate (ketogenic), low-carbohydrate (LC) and low-fat (LF) diets have shown some success and have been well tolerated in promoting short-term weight loss, both in children and adults (100;101). Researchers have concluded that the LC diet appears to be an effective technique for short-term weight loss in overweight adolescents and does not detrimentally affect the lipid profile (102). Astrup et al. were mainly interested in determining the nature of dietary components in subjects who consume fat and carbohydrate and demonstrate a positive energy balance. Participants who were exposed to high-fat foods for several weeks tended to over consume energy, explained by the relatively energy-dense nature of high-fat foods, compared lower fat foods. This overeating effect has been termed passive overconsumption (103). The stimulatory effect of fatty foods on energy intake depends not only on their high energy density, but also on the possible effect fat has in the mouth. The passive overconsumption effect of dietary fat on energy intake occurs during consumption (i.e. it is an intra-meal effect). Therefore, explaining why fat has a comparatively weaker effect on satiety than other foods for a given amount of energy consumed. Many short-term studies on appetite and energy intake clearly corroborate this, showing that fat is less satiating than carbohydrate and protein, and that high-fat foods are more likely to encourage passive overconsumption and weight gain than low-fat foods (104). The comparative contributions of

carbohydrate sources in the diet may have possible implications for body weight regulation and obesity. The main dietary alteration in recent times has been the increase in fat intake at the expense of carbohydrates. An inverse relationship between dietary fat and carbohydrate has been established in several cross-sectional studies in countries of widely varying socio-economic status. In addition, modern diets tend to include more simple sugars, at the expense of more complex carbohydrates, which tend to balance the fat energy of the diet. This phenomenon has been called the 'fat-sugar seesaw'. The Scottish part of the Monica Survey has delivered the largest dataset related to this, which clearly showed an inverse relationship between sugar intake and obesity (105). It has long been argued that a reduction in total fat intake occur hand-in-hand with a rise in carbohydrate intake, and this may lead to an increase in plasma triglycerides and a decrease in plasma HDL-cholesterol, in turn increasing the risk of coronary heart disease (CHD). It has also been proposed that mono-unsaturated fat has a more positive effect on risk factors for CHD than carbohydrate does. However, the carbohydrate source and the glycaemic index might have an important role for the effect on risk factors. Both observational and interventional studies demonstrate that a low glycaemic index diet exerts more beneficial effects than a high glycaemic index diet in terms of insulin resistance, LDL- and HDL-cholesterol, and plasminogen activator inhibitor-1 activity (106;107). Therefore, the high carbohydrate content of low-fat diets should come mainly from the complex carbohydrates such as vegetables, fruits and whole grains, which are more satiating and contain fewer calories than fatty foods. At the same time they offer a good source of vitamins, minerals, trace elements and fibre. A high fibre diet can not only improve the satiating effect of the diet, but also delivers a beneficial effect on blood lipids and blood pressure levels, especially if the diet is rich in soluble fibre, such as oat bran, legumes, barley and most fruits and vegetables (104). A large body of experimental data still suggest that protein exerts a greater satiating power per calorie than carbohydrate and fat in adults. So, in conclusion, the available evidence suggests that a diet with a protein content representing up to 25% of energy may be helpful for weight regulation in adults (104).

1.4.1.2 Diets and Exercise

Many studies (Appendix 2) (93), including Curioni and Lourenco have examined diet and exercise (83) and their systematic review; which evaluated a total of 33 trials evaluating diet, exercise, or diet and exercise in combination. Only 6 studies were found that directly compared diet and exercise with diet alone. The active intervention period ranged between 10 and 52 weeks across studies and a 20% greater initial weight loss was achieved by the diet and exercise group of studies (13.0 kg vs. 9.9 kg). The combined intervention also resulted in a 20% greater sustained weight loss after 1 year (6.7 kg vs. 4.5 kg), than diet alone. In both groups, almost half of the initial weight loss (50%) was regained after a year (83).

1.4.1.3 Psychological Cognitive Behaviour Therapy (CBT)

Lately a new cognitive behavioural therapy (CBT) method for the treatment of obesity has been developed, which is comparable in style and strategy to CBT for Bulimia Nervosa (108;109). It targets those patients who overeat and have a low level of activity, emphasising processes that help in weight maintenance (110-112). As per Cooper et al., most of the participants lost weight and then regained it (110;112). For people with obesity it is remarkably hard to maintain weight loss. Though evidence of weight loss maintenance exists (113;114), it is uncommon, and no convincing explanation exists. Persistent changes to behaviour are hard to achieve in people with obesity, as compared to people with eating disorders (115). Binge eating disorders in patients with obesity improved significantly in a combined approach, comprising diet, exercise and CBT. Exercise appears to offer added value to the nutritional CBT, leading to improved mood, recovery from eating disorders and weight loss (116). Additional studies and long-term data are needed to determine whether psychological treatments for obesity are truly effective.

1.4.1.4 Anti-obesity drugs and supporting diets

In the 1990s, the combination of fenfluramine and dexfenfluramine proved that significant weight loss and weight loss maintenance is possible with medication. However, the combination was withdrawn from the market due to increased risk of damage to heart valves (117). In 2000, the European Medicines Agency (EMA) withdrew phentermine, diethylpropion, and mazindol, because of a perceived unfavourable risk-to-benefit ratio (118). The first selective CB1 receptor antagonist, rimonabant was licensed in 56 countries from 2006, but it was never approved by the U.S. Food and Drug Administration (FDA) because of unfavourable psychiatric events, such as depression, anxiety, and suicidal ideation (119). Rimonabant was withdrawn from the European market in 2009. Sibutramine was approved by the U.S. FDA in 1997, but was withdrawn in October 2010, due to its association with increased cardiovascular risk and stroke in patients with established cardiovascular disease as demonstrated by the results of the SCOUT trial (120). This was disappointing as the SCOUT trial specifically recruited patients that were, until that point, contra-indicated from treatment with sibutramine and there was no evidence of harm in the group of patients that were treated according to the licence of the drug. This left orlistat as the only approved pharmaceutical option for obesity for several years. After initial concerns in 2011 regarding possible cardiovascular risks (121), the FDA approved the combination of bupropion and naltrexone (Contrave®) in September 2014 for obesity management (122). In 2013, the FDA approved Qsymia® a combination of phentermine and topiramate extended-release (123). They also approved liraglutide a GLP-1 analogue for weight loss especially as the drug was already approved for the treatment of T2DM. The evaluation of the long-term safety and efficacy of newly-developed drugs for obesity is proving difficult. Obesity frequently needs continuous treatment to achieve and maintain weight loss, although the inflexibility of the regulatory system for the endorsement of novel anti-obesity drugs and the regulatory guidelines for anti-obesity treatment are limiting drug development. Given the poor safety track record of obesity drugs, the approach of regulatory bodies is understandable, but frustrating (121).

Orlistat

Orlistat is a reversible gastrointestinal lipase inhibitor which reduces calorie absorption by attenuating hydrolysis of dietary fat in the gut (124). A meta-analysis of twenty nine studies showed that orlistat decreased body weight by only 2.6 kg at six months and 2.9 kg at twelve months (125). Waist circumference, blood pressure, total cholesterol, and LDL-C were reduced, while glycaemia and insulin resistance were improved (126-128). The effects of a high fat diet, when taken in combination with orlistat, are unpleasant and include diarrhea, steatorrhea, flatulence, bloating, dyspepsia and abdominal pain (129). It is important to note these effects, particularly in discussion with patients, since understanding this crucial information may help to avoid poor compliance among patients upon early negative experiences of side effects. If explained appropriately, then the drug may result in a change from “mindless eating” to “mindful eating” with patients changing their diet to consume fewer calories from fat and avoid steatorrhea. A deficiency of the fat-soluble vitamins (vitamin A, D, E, and K) is rare and, although no evidence exists to show either positive or negative effects, definitive data on long term cardiovascular outcomes are still awaited (130). In combination with a low fat diet, orlistat reduces weight and prevents weight regain, while also improving some obesity comorbidities (131). The XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects) study compared weight loss and new incidence of T2DM over four years in patients with obesity and impaired glucose tolerance. Patients were randomised to lifestyle changes plus either orlistat or placebo (126). Orlistat combined with lifestyle modification was better for weight loss and T2DM prevention, compared with lifestyle modification alone (126). The X-PERT study showed good weight loss and reductions of the components of the metabolic syndrome when lifestyle changes were combined with diverse dietary interventions and orlistat (132). A systematic review and meta-analysis of ten studies to assess the effects of orlistat on cardiometabolic risk factors (133) offered similar findings to those of a multicentre randomized double-blind placebo-controlled study (RCT) comparing orlistat to placebo. All groups had a nutritionally balanced diet with a 600-kcal energy

deficit. The orlistat groups lost significantly more weight and maintained the weight loss over two years (134).

Orlistat drug interactions

Vitamin K absorption may be impaired, and hence warfarin anticoagulation may be potentiated, as a result of orlistat therapy (135). Patients on stable warfarin doses who start orlistat should have more frequent international normalized ratio (INR) monitoring initially. Other possible drug interactions include a decrease in the absorption of amiodarone (136) and cyclosporine (137).

Contrave®

Contrave® is a combination of naltrexone sustained-release (SR) and bupropion (SR), which are a norepinephrine/dopamine reuptake inhibitor and an opioid receptor antagonist, respectively. These drugs are licenced separately for depression and smoking cessation, but both have been associated with weight loss (121). In almost all studies, the Contrave® group demonstrated a significant weight reduction and improvement in cardiometabolic markers when compared to the placebo group. The COR-Diabetes trial showed, that after 56 weeks patients with T2DM and overweight or obesity lost more weight and achieved better improvement in glycaemic control than those who were treated with a placebo (138). All these patients had simultaneous intensive behaviour modification (BMOD), portion size control, calorie counting, detailed daily food intake recording and increased physical activity. Patients were instructed to consume a balanced low calorie diet with 15–20% of energy from protein, 30% or less energy from fat and 50% from carbohydrate. Group sessions were conducted by dietitians, behavioural psychologists, or exercise specialists weekly during the first four months of the study, followed by monthly sessions thereafter. A combination of Contrave® with the intensive BMOD produced significantly greater weight loss than BMOD alone (139).

Qsymia

Qsymia (Qnexa®) is a combination of low-dose phentermine and the antiepileptic agent topiramate(140). The combination has been shown to maintain an approximately 10% body weight loss. The drug is intended to complement lifestyle modification, a low fat diet, exercise, behavioural changes and surgical approaches (123;141). Within trial settings, the drug has been combined with the LEARN (Lifestyle, Exercise, Attitudes, Relationship, and Nutrition) Program for weight management (142), which included a balanced 500kcal reduced diet. Patients were also offered nutritional and lifestyle modification counselling (141-145).

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue that was first used to treat T2DM. As GLP-1 suppresses appetite and delays gastric emptying, it was found that liraglutide reduces body weight in non-diabetic patients (146). Higher doses of this drug can produce better weight loss, which may reach 10 kg in 2 years (146;147). The drug was combined with a 500 kcal reduced diet (30% of energy from fat, 20% from protein and 50% from carbohydrates) alongside increased physical activity (148).

Diet to support anti-obesity drug

Pharmacotherapy can be useful for treating obesity as a part of a comprehensive approach, which includes lifestyle modification (149;150), diet, exercise, and behavioural therapy (132). The most successful strategy to use alongside pharmacotherapy initially is the low calorie diet (LCD), comprising an intake of 800 to 1500 kcal/day, or a balanced-deficit diet typically around 1500 kcal/day, which can result in approximately 8% body weight loss over six months. An Expert Panel, convened through the National Institutes of Health/National Heart, Lung, and Blood Institute, on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, suggested a 500 to 1000 kcal/day deficit diet for people with obesity, aiming at 0.5 - 1 kg weight loss per week. However it remains challenging to determine patients' daily energy requirements and thus calorie-intake

guidelines are often based on a patient's original body weight(151). Regular adjustment of the calorie content of any prescribed diet is needed in response to a patient's weight-loss response and treatment goals. Low-fat diet was the typical approach (152), but an increase in proteins and low glycaemic index carbohydrates, may be equally helpful (88). It has been shown that people with obesity who achieve long-term weight maintenance consume only 25% of their calorific intake from fats (153). A low carbohydrate ketogenic diet (LCKD) has been shown to lead to improvements comparable with those of orlistat plus low-fat diet (O+LFD) (154;155).

This LCKD restricted carbohydrate (CHO) intake at first to less than 20 g/d (154;155). This diet permitted high fat intake, with patients allowed *ad libitum* to eat meat, eggs, hard cheese, low-carbohydrate vegetables (e.g. leafy greens), and moderate-carbohydrate vegetables (e.g. broccoli, asparagus) daily, with no restrictions on calorie intake. Approximately five grams from other CHO was added to their intake per day each week as they approached their target weight or if cravings threatened their compliance. A second group received orlistat (120 mg orally 3 times before meals per day), plus a LFD, with fat constituting <30% of daily energy, saturated fat <10% and containing <300 mg cholesterol per day. The study showed that both the very high-fat (i.e. the LCKD) and the very low-fat diet had similar health benefits. Brinkworth et al. (156) also confirmed that compliance with a low-carbohydrate diet can be maintained for 1 year. The combination of orlistat with a LCKD has not been tested. Weight loss was considerably greater in patients who regularly attended group sessions. This selected population may represent the more motivated patients, or it may be that sessions had a positive motivational effect upon patients attending, or indeed a combination. Incorporating intensive weight loss programs into medical practice and identifying suitable patients requires extra effort from healthcare providers, which may not always be possible (157). Reduction in energy intake is the cornerstone for reducing weight, while appropriate nutrition counselling, behaviour modification therapy and lifestyle changes could aid weight loss maintenance, adding

medications to reduce long term calorie intake might have additional benefits, such as improving T2DM, cardiovascular risk, hyperlipidaemia, and sleep apnoea (158).

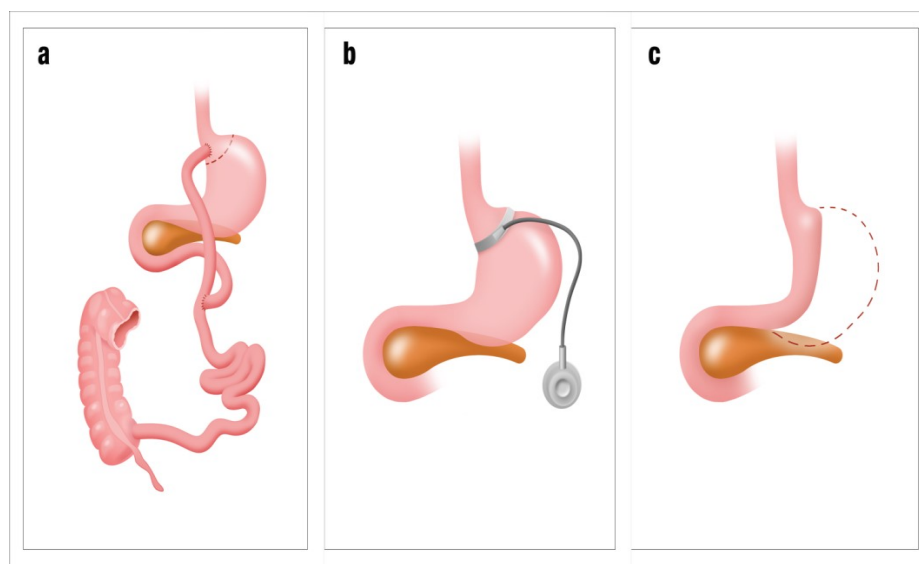
1.4.2 Surgical Treatment

1.4.2.1 Types of bariatric surgery

Bariatric surgery, like all other surgical interventions, was developed through the contribution of many experts (159). The first breakthrough that was led by Drs. Arnold Kremen and Richard Varco, surgeons at the University of Minnesota, who recognised that severe obesity, was a disease dangerous enough to warrant surgery. Based on the understanding they gained from their experience with the “short gut” syndrome, they were able to develop the intestinal bypass, a technique that eliminates the majority of the small intestine from interaction with food. They established, across numerous procedures, that an end-to-end anastomosis from 36 cm along the jejunum to the final 10cm of ileum, with the excluded segment draining into the sigmoid colon, provided the greatest expected weight loss. The second major breakthrough came with the cautious investigations of Dr. Edward Mason, also a member of the Minnesota group, who recognised that weight loss could be attained just as successfully, and far more safely, through two gastric procedures, the gastric band and the gastric bypass(160). These two operations continue as the most broadly performed bariatric procedures in the world today (161). The third innovation was the documentation by Pories et al. (162) and MacDonald et al. (163), with very impressive 95% follow-up of 608 patients for up to 16 years, that the gastric bypass procedure not only led to weight loss of more than 45 kg, but also controlled comorbidities, including T2DM, and reduced mortality. A fourth main development was the demonstration in 1994, by Wittgrove and Clark (164), that the gastric bypass, as an invasive abdominal surgical operation, could be performed using a laparoscopic approach, improving its safety and reducing the associated trauma. The fifth remarkable shift was the introduction of quality control of bariatric surgery on a national basis and the demonstration that these operations can be done with very low rates of mortality and morbidity

in centres with high capacity and experience. An example of this is the American Society for Bariatric and Metabolic Surgery (ASMBS), which rolled out a program for the certification of Bariatric Centres of Excellence (165). Bariatric surgical procedures that modify the anatomy of the gastrointestinal tract reduce caloric intake as a result. Operations have historically and possibly wrongly been categorised as either 'restrictive' or 'malabsorptive'. 'Restrictive' procedures were said to work by limiting the food intake by means of reduction in the volume of the gastric reservoir, along with a narrow outlet to delay emptying, such as in the case of the gastric band. "Malabsorptive" procedures bypass varying portions of the small intestine, where nutrient absorption take place (166), and were therefore thought to reduce the proportion of calories that could be extracted from ingested food. Procedures thought to limit intake and produce malabsorption concurrently, were classified as 'mixed' procedures, such as the gastric bypass and duodenal switch(167).

Figure 1.4.2-1 Types of Bariatric Surgery



Bariatric Surgery a. Roux-en-Y gastric bypass, b. Adjustable gastric banding and c. Vertical sleeve gastrectomy.

Restrictive procedures include gastric stapling (gastroplasty) and adjustable gastric banding or a combination of these two approaches. Adjustable gastric banding (AGB) is performed by wrapping a synthetic, expandable band around the stomach to create a small pouch with a narrow outlet. It also includes the insertion of a subcutaneous reservoir, continuous with an inflatable portion of the band, so that gastric restriction can be adjusted by means of saline injections. AGB is performed laparoscopically, and the band is removed during a second laparoscopic procedure (Figure 1.4.2-1-b) (168). Another more recently developed procedure is the vertical sleeve gastrectomy (VSG) (Figure 1.4.2-1-c), in which resection of much of the gastric body along its greater curvature, leaving a narrow tube of stomach as an alimentary channel, with around 75% of the stomach removed (166). Proximal Roux-en-Y gastric bypass (RYGB) (Figure 1.4.2-1-a) is often referred to as a mixed procedure. It includes stapled transection of the stomach to produce a small (~25 ml) upper gastric pouch.

The small intestine is divided approximately 70-100 cm along the jejunum, and the distal portion (called the alimentary, or Roux limb) is anastomosed to the gastric pouch as a gastrojejunal (GJ) anastomosis. The proximal part of the jejunum remains in continuity with the duodenum and distal part of the stomach, as the biliopancreatic limb. This limb drains digestive juices from the stomach, liver, gallbladder and pancreas downstream, where its end is anastomosed, end-to-side, to the jejunum of the alimentary limb as a jejuno-jejunal (JJ) anastomosis, approximately a further 70-100cm distal to the GJ anastomosis. The result is a Y-shaped Roux construction – referred to as the Roux-en-Y construction - whereby undiluted gastric, biliary and pancreatic secretions meet ingested food approximately 150 to 200cm along the jejunum at the JJ anastomosis. The intestine beyond the JJ anastomosis is referred to as the common channel. The shorter this common channel is (and therefore the longer the Roux limb), the greater the effect is likely to be on weight loss, but also micronutrient deficiency (169). A balance must, therefore, be struck. True calorie malabsorptive procedures include biliopancreatic diversion (BPD), often performed as a variant procedure called duodenal switch (DS), which incorporates a vertical sleeve gastrectomy. Some surgeons perform

a sleeve gastrectomy as phase one of a two-staged operation, performing a Roux-en-Y gastric bypass procedure after initial weight loss has made surgery less challenging and reduced the operative risk (166). It was stated that in 2008 worldwide approximately, 344,200 bariatric surgery operations were performed by 4,680 bariatric surgeons; approximately 220,000 of these operations were performed in USA and Canada by 1,625 surgeons. At the time the most commonly performed procedures were LAGB with 42.3%, laparoscopic RYGB with 39.7%, and vertical sleeve gastrectomy (SG) with 4.5%, and over 90% of all procedures were performed laparoscopically (170). These trends have now changed with the gastric band becoming less popular and the sleeve gastrectomy more popular. Bariatric surgery has increasingly been identified as metabolic surgery, as all procedures for weight loss, whether described as restrictive, malabsorptive, mixed, or other, involve neuro-hormonal mechanisms. Buchwald proposed a definition of metabolic surgery in 1978 as: "the operative manipulation of a normal organ or organ system to achieve a biological result for a potential health gain" (170).

Bariatric surgery's primary goal is the improvement of obesity-related medical problems. Its outcomes should be evaluated in terms of both significant weight loss and improvement of obesity related medical disorders (171). It has been documented that bariatric surgery in morbidly obese patients' reverses, eliminates, or significantly improves diabetes, hypertension, hyperlipidaemia, and obstructive sleep apnoea. These benefits will take place in most patients who undergo weight loss surgery (172). Two studies by Schauer et al. (173) and Sugerman et al. (174), have reported almost matching rates of resolution of T2DM as in a meta-analysis did; 83% and 86%, respectively. In addition, after 2 years of follow-up, a 60% reduction in plasma insulin and a 20% reduction in the plasma glucose were seen in the surgical weight loss group of the Swedish Obesity Subjects study (SOS) (175). The control group at 2 years had a 3.7-fold higher risk of diabetes onset. Diabetes often resolves in days following bariatric surgery, even before noticeable weight loss occurs (162). In addition, improvement or resolution of hypertension is also observed. In the present

analysis, improvement in obstructive sleep apnoea was 80% or even higher range. Overall wellbeing, social function, self-confidence, body self-image, ability to interact with others, and spending time in recreational and physical activities also improve after successful bariatric surgery. Productivity and economic opportunities are better, with new employment and greater employment satisfaction. Generally all therapeutic interventions balance effectiveness against risk. In such evaluation, bariatric surgery fares extremely well. The operative 30-day mortality rate is around 0.1% for restrictive procedures, 0.5% for gastric bypass, and 1.1% for biliopancreatic diversion or duodenal switch associate positively with the accepted operative mortality rates as compared with other major surgical procedures (172). After 2 years, most patients reach their maximum weight loss. Thereafter, patients often experience a slight regain of weight by the fifth year, in the order of 5–7%, followed a steady reduction again over the subsequent years (161). According to Evola et al. and other groups, it was concluded that bariatric surgery is capable of resolving pathology that has previously been considered irreversible by endocrinology specialists, dieticians, internists and psychologists. Despite this, it is essential to study the potential complications of bariatric surgery. It is important to point out that some patients require a further operation following bariatric surgery, often for internal hernia, or gallstone disease. In a very small group, reversal of procedure is required for uncontrolled nutritional deficiency, although this is generally restricted to the more aggressive, less common procedures such as BPD(176). The standardization of bariatric surgical procedures and care has likely contributed to a reduction in mortality rates. Nevertheless, the complications after bariatric surgery can be lethal and may require urgent treatment by suitably experienced surgeons, familiar with these complications. These complications can be classified into two groups: acute and long-term. Acute complications, which may occur in 5–10% of the patients, depend upon the procedure, patient age, and other pre-operative risk factors, and are similar those encountered after other abdominal operations, *i.e.* haemorrhage, anastomotic leak, infection, obstruction, arrhythmia, and pulmonary emboli. Because of excess weight, rhabdomyolysis may also see, particularly after prolonged operations.

Surgeons with limited experience of long-term complications after bariatric surgery may struggle in managing them. Such long-term complications include neuropathies due to nutritional deficiencies, internal hernia, anastomotic stenosis, and emotional disorders. Though a daily chewable multi-vitamin and mineral supplements will help in avoiding potential nutritional deficits (167).

1.4.2.2 Bariatric surgery in adolescents

Bariatric surgery is now being considered as a possible paediatric intervention, for the same reasons that it has proven effective in adults. The dramatic increase in obesity prevalence has occurred not only in adults, but also in young people (177), illustrating the need for effective preventive measures, and beginning early in life to improve dietary habits and increase physical activity. Bariatric surgery is presently considered as a “rescue” approach for patients with severe obesity (178). Previously, 18 to 65 years was the age limit for such surgery, but recent data have showed that adolescents and the elderly (≥ 70 years) may also benefit from this kind of surgery, with little or no increase in risk (167). Most of the evidence proves that nonsurgical methods such as diet and exercise for weight control have failed to achieve sustained weight loss in young people with severe obesity (179). Available studies with hypocaloric diets, very-low calorie regimens, exercise, behaviour modification and pharmacological agents have demonstrated ineffectiveness. Studies that have lasted for longer than 1 year have been few in the literature until recently. In a study of 1,187 young people, evaluating a hypo-caloric diet and orlistat (180) of the subjects receiving a hypo-caloric diet alone, 295 withdrew within 4 weeks of the start of the programme. Of the remaining 892 subjects, 668 received orlistat plus the hypo-caloric diet, only 306 (46%) of whom completed the study. From the limited group of subjects completing the study, an average of 5.56 kg was lost across 2 years (181). As per Inge et al. the initial experiences with surgical treatment for adult obesity were first published in the late 1960s (182;183). During the 1970s and 1980s the bariatric procedures for young people with severe obesity were first described. Bariatric procedures such as jejuno– ileal bypass were performed on at least 20 young people (age range 11–20 years) with a preoperative weight of

≥120 kg (184;185). The procedures resulted in 34–36% weight reduction among these subjects. Significant improvements in T2DM, hypertriglyceridemia and general quality of life were also reported. However, fat soluble vitamin deficiencies, electrolyte abnormalities and diarrhoea also were common. Reversal of the jejuno–ileal bypass was necessary for many patients in response to these nutritional complications(184;186). As a result of the high risks associated, this procedure is no longer used (187) in the treatment of adult and adolescent obesity (188-190). Biliopancreatic diversion (BPD) was also performed for small number of young people, involving a partial gastrectomy and bypass of a large portion of the small bowel. However, this operation carries a high risk of postoperative protein and micronutrient deficiency (191). Specific complications have included hypoalbuminaemia, deficiencies of vitamins A, D and folic acid. It was suggested that such malabsorptive procedures should not be considered first-line among weight loss procedures for young people. Between the early 1980s and mid 1990s surgeons developed the vertical-banded gastroplasty (VBG) as an alternative procedure (160;192;193). Following on from the VBG, the vertical sleeve gastrectomy (VSG) was subsequently developed and is increasingly being used both in adults and adolescents. Mean BMI decreased by 25% at 5 years and 22% at 10 years after VBG (160). Adult patients who have undergone VSG alone have lost significant weight (approximately 25%) over a 6-month period, with few nutritional side effects (194). Longer-term follow-up is needed to determine the relative benefits and risks of the VSG compared with other procedures (195). RYGB has been used for weight loss in the US since 1960s for adults and the 1980s for young people (191;192;196). The largest retrospective study of adolescent bariatric surgery with the longest follow-up to date was provided by Sugerman et al. over a 21-year period between 1981 and 2002, thirty-three adolescents underwent different types of procedures including 30 with RYGB and 3 with horizontal or vertical gastroplasty (197). Mean preoperative BMI was 52 kg/m² with mean age of 16 years. Major complications observed within a month of the procedure comprised one major wound infection, one pulmonary embolism, three stomal stenoses requiring endoscopic dilation and four ulcers within the Roux limb-treated medically. Late (beyond one month) complications comprised

one small bowel obstruction and six incisional hernias. Two late deaths occurred, one at 1 year and one at 6 years. Although post-mortem was not performed after either of these sudden deaths, it was thought that these deaths were unconnected to the surgical procedure. Results have also shown that all preoperative comorbidities had resolved at 1 year except for gastroesophageal reflux and hypertension in two patients each. Mean BMI, measured at 1, 5, 10 and 14 years after surgery, was 36, 33, 34 and 38 kg/m², respectively. Only five patients (15%) regained all or most of their lost weight at 5–10 years after surgery (197). Generally, in young people who have completed linear growth, a BMI of 40 kg/m², or 35 kg/m² with obesity-related co-morbidities, can be used as eligibility criteria for surgical intervention for obesity (198).

AGB is another procedure explored in the treatment of obesity (199). An Australian adolescent series is considered the largest to date, consisting of 41 young people (age range 12–19 years) with a mean weight of 125 kg, and a mean BMI 42 kg/m². Weight loss in the region of 30% was reported 3 years postoperatively among the 18 patients, with 3-year data available. All patients' comorbidities improved and few complications were reported during follow-up. One patient experienced gastric prolapse (band slippage) needing band repositioning, and one experienced a leak from the tubing requiring a revision procedure. RYGB achieves greater weight loss and comorbidity resolution, as compared to AGB, at 1–3 years (200;201), although comparable weight loss has been shown at later (5 year) time intervals 33 (198). Tsai et al. have recently examined the temporal trends in utilization of bariatric surgery in young people, using the National Inpatient Sample, a large US administrative database (202). Over 3000 bariatric procedures were carried out for young people between 1996 and 2003. Around 200 cases per year were initiated between 1996 and 2000. From 2000 to 2003 however, the use of weight loss procedures in young people increased up to three-fold, with gastric bypass accounting for around 90% (203). Since then, VSG has begun to catch up with RYGB in popularity. While there appears to be a good foundation to support bariatric surgery in young people, the associated nutritional risks must also be considered and explored in the long term (204).

There is potential for inadequate absorption of calcium, iron, folate, vitamins B1, B6, B12, A and vitamin D, especially in the absence of micronutrient supplements (205-208). Even procedures which cause no micronutrient malabsorption might result in reduced consumption of macro and micronutrients with possible risks for young people. Up-to-date supplementation practices are often founded upon standards established in adults, in whom regimens often differ from one surgical centre to another. Reliable evidence to inform doses and types of nutritional supplementation is lacking. The increased length of time the young people are expected to live with altered physiology and anatomy, as well as perceived poor compliance during this critical developmental period represent additional difficulties that are not usually seen among adult bariatric candidates. Optimum supplementation regimens must be determined (198).

1.4.2.3 Safety and ethics of bariatric surgery in adolescents

The performance of bariatric surgery in paediatric patients raises significant ethical questions. The central ethical matters before deciding on a bariatric procedure for an adolescent obese patient are whether the patient's health is being compromised by morbid obesity, and whether comorbidities are treatable by less invasive means. Surgery is generally not considered in adolescents unless the patient has tried conservative measures but failed. An additional important consideration is the patient's ability to demonstrate decisional capacity (177). The adolescent patient with obesity and their family should receive extensive preoperative counselling and give informed consent. Additionally, the bariatric team should have a comprehensive system of short-and long-term care in place (209). Capacity to make decision is not determined strictly by chronologic age. A 13 year-old adolescent obese patient, if developmentally normal, might be able to make informed decisions. Thereafter the multidisciplinary bariatric team should determine collectively whether they believe the patient has capacity, clearly documenting as such. Patients with decisional capacity must be allowed to contribute to decisions regarding their care (177).

1.4.2.4 Vertical Sleeve Gastrectomy

VSG is a relatively recent procedure, with an advanced learning curve. In a randomized prospective study comparing the results of AGB and VSG after 1 and 3 years of follow-up (210), the median weight loss after 1 year was 14 kg for AGB and 26 kg for VSG; and after 3 years 17 kg for AGB and 29.5 kg for VSG. The median decrease in BMI after 1 year was 15.5 kg/m² for AGB and 25.0 kg/m² for VSG; and after 3 years were 18.0 kg/m² for AGB and 27.5 kg/m² for VSG. The percentage excess weight loss (%EWL) at 1 year was 41.4% after AGB and 57.7% after VSG; and at 3 years was 48% after AGB and 66% after VSG. The improvement in feelings of hunger after 1 year was noted in 42.5% of the patients with AGB and 75% of the patients with VSG; and after 3 years this decreased to 2.9% in the AGB group and 46.7% after VSG. Craving for sweet eating was improved, albeit not significantly so, after 1 year in 35% within the AGB group and in 50% in the VSG group; and after 3 years these numbers decreased to 2.9% in the AGB group and 23.3% in the VSG group. These study results at 1 year after VSG are comparable to those reported by Langer (211), Baltasar (212) and Johnston (213). The first factor accounting for the differences between the two procedures in terms of weight loss and of improvement in hunger sensation is the difference in hormonal effects between the procedures. Ghrelin, an acylated upper gastrointestinal peptide, is an orexigenic hormone whose circulating levels rise before meals, stimulating hunger, and fall after eating, with a corresponding cessation of hunger (214). VSG also contributes to reduced stimulation of the hunger centre because of removal of the gastric fundus. One limitation of restrictive surgery is related to “sweet eating”, which seems to continue after the procedure. Craving for sweets has been shown to return after 3 years, more so for AGB than for VSG (210). VSG is intended to reduce appetite by decreasing the volume of the stomach, producing a sense of fullness after reduced oral intake (166;212;215-217). Initially, gastrectomy was performed for the resection of gastric neoplasms, before its subsequent adaption for bariatric surgery, taking advantage of the significant weight loss observed as a side effect (218). Johnston et al. (213) described a similar gastric division without resection for weight

loss that was called the Magenstrasse and Mill procedure. As a weight loss procedure, VSG was first defined by Hess and Marceau et al. (219;220) as part of the biliopancreatic diversion – duodenal switch (BPD/DS) surgery. In 2000, Ren et al. (221) described performing this surgery completely laparoscopically, and subsequently defined VSG as the first of two stages for high-risk obese patients (222). It was later proposed that VSG constitutes an easier, faster, and hence safer procedure in these high-risk patients than RYGB, BPD or DS (223). Baltasar et al. suggested that good candidates for VSG include the super-obese (BMI>55), as a first stage for the laparoscopic DS; class III obese patients (BMI ≥40) with severe medical disease such as cirrhosis, or Crohn's disease; patients with lower classes of obesity profoundly affected by co-morbid conditions; patients who have previously undergone AGB and subsequent band removal; and, finally, the morbidly obese adolescent. Following VSG, it is possible that the remnant stomach may expand or that gastric emptying may slow down again. In this situation, performing a second sleeve gastrectomy is still an option (224), although many bariatric teams would consider RYGB as the next option. A large body of evidence determined that VSG may be a definitive weight loss procedure for some patients. It is typically considered a technically less challenging procedure than RYGB and BPD/DS, and can achieve both impressive weight loss and reversal of obesity-related comorbidities. Since VSG is a restrictive procedure, so it appears to lead to fewer nutritional concerns compared with more malabsorptive weight loss procedures and many patients do not appear to need additional procedures. VSG is being increasingly performed around the world and, as evidence builds regarding its long-term effects on weight loss and its maintenance, researchers have suggested that this surgery will be broadly adopted in the future (223).

Numerous advantages for the VSG have been presented in the literature: 1) stomach volume reduces without significant impact on function, so most food items can be consumed, though in lesser amounts; 2) the stomach portion that is believed to be associated with the hunger stimulating hormone, ghrelin, is removed; 3) dumping syndrome doesn't occur since the pylorus is preserved;

4) the chance of developing a peptic ulcer is reduced; 5) avoiding the intestinal bypass helps reduce risks of intestinal obstruction, osteoporosis, anaemia, protein and vitamin deficiencies; 6) it is an effective first-stage procedure for patients with high BMI (BMI>55 kg/m²); 7) It seems, according to the limited results in the literature, to be a promising standalone procedure for patients with low BMI (BMI 35-45 kg/m²); 8) it is a tempting choice for people with existing anaemia, Crohn's disease or other conditions that increase the risk of intestinal bypass procedures; 9) it can be performed laparoscopically in patients that are >225 kg of weight; 10) no foreign body is introduced; 11) the operative time is relatively short compared to other procedures; 12) patients recover easily; 13) relatively few associated side-effects; 14) it is a substitute for the AGB and gastric balloon that need recurrent adjustments and are foreign bodies as well; 15) in the case of inadequate weight loss, progression to RYGB or DS are still feasible 16) it is a very good procedure for morbidly and super-obese young people, in whom some would argue more aggressive surgery should be avoided (224;225). On the other hand some disadvantages of the VSG have been recognised: 1) the possibility of insufficient weight loss or weight regain (although this may occur in all weight reduction procedures, especially with operations that do not involve an intestinal bypass); 2) patients with higher BMI may require a second-stage operation in the future to help them lose the remaining excess weight. This may be safer for high BMI patients than performing a single operation with a greater physiological burden; 3) soft, easily absorbed calorie-dense foods, such as milkshakes, ice cream and melted chocolate, can be still consumed in high volumes, counteracting weight loss effects; 4) gastric staple line leakage and other complications associated with stapling may take a place; 5) the procedure is non-reversible because of stomach removal, but practically it can be converted to any other weight loss procedure; 6) some surgeons and insurance companies still considers it as investigational procedure; finally 7) results from long-term follow-up are not available yet (224;225).

1.4.2.5 Vertical Sleeve Gastrectomy in adolescents

VSG is emerging as a standalone procedure in adolescents (222). From 1997 to 2003, the volume of

adolescent bariatric surgery performed in the United States was projected to have increased 5-fold, from 51 to 282 (226). Data from a global survey indicated an increase in the use of VSG from 0% of all procedures in 2003 to 5.4% in 2008 (170). Results from 15 studies of VSG including 940 adult subjects revealed excess weight losses (EWL) of 46% to 83% 1 year after surgery (227), with reports of weight loss maintenance up to 5 years after surgery (228). A 6-year follow-up for a total of 30 patients who underwent VSG showed a mean (EWL) of > 50% (229). The majority of studies reporting consequences after VSG involve adult patients. VSG for treating severe obesity in young people has been reported. A small study of adolescents patients (n=7) revealed weight loss in 6 of 7 patients, improvement in comorbid conditions and no operative complications (230). Another small study (n=4) established similar findings with no postoperative malnutrition or vitamin deficiency (231-235). Nineteen young patients in the USA, aged 13-17, underwent vertical banded gastroplasty or RYGB between the period between May 1990 and August 2001. The average BMI was 49 kg/m² and almost all patients had one or more co-morbidities. Follow-up was completed to 10 years. Treatment was considered to have failed in only one participant, who failed to lose sufficient weight. In addition, two patients required surgical revision, but no mortality or morbidity was reported. The emerging body of evidence suggests that an early surgical intervention must be accessible to a larger number of young people to minimize the emotional and physical consequences of morbid obesity (181). A recent study of a larger series of young people undergoing VSG between March 2008 through February 2011 was published by Al Qahtani et al. the group reported data from 108 patients aged 5 through 21 years. Patients attended follow-up visits at 3 (n = 88), 6 (n = 76), 12 (n = 41), and 24 (n = 8) months postoperatively and experienced median EWL of 28.9%, 48.1%, 61.3%, and 62.3%, respectively. No serious postoperative complications were reported. Available co-morbidity data pointed out improvement of dyslipidemia in 70%, hypertension in 75%, prehypertension in 83%, obstructive sleep apnoea in 91%, diabetes in 94%, and prediabetes in 100% (236). Al Qahtani published a recent updated data for 226 paediatric patients and concluded that VSG resulted in successful short-term weight loss among paediatric patients. Additionally, improvement or remission of 90.3% of

comorbidities was reported, 64.9% of which were within the first 12 weeks after surgery. No further improvement or remission was observed beyond 2 years, and there was no recurrence up to 3 years in patients who were seen in follow-up. The loss to follow-up in each of the 3 years was 4.2%, 7.6%, and 15.3%, respectively (237). Long-term data are needed for better understanding and evaluation of the maintenance of weight loss, especially into adulthood (236;237). The most up to date study was published by Al Sabah et al., with a total of 135 adolescent patients underwent VSG were followed up for an average of twenty months. The patients had a median age of 19 years (range 12-21) and a mean BMI of 48.5 kg/m². The %EWL at 2 years for males and females was 84 and 77%, respectively. All patients with T2DM and 75 % of those with hypertension demonstrated complete resolution at 2 years (238). Al Qahtani and colleagues described several concerns and disagreements surrounding the use of bariatric surgery for weight loss in severely obese young people. In a recent report of a randomized controlled trial (RCT) comparing LAGB with lifestyle changes in adolescents, O'Brien et al (239) encourage the reversible LAGB over irreversible procedures, stating that "better therapies are likely to become available during the active life of the adolescent".

Al Qahtani's review voiced disagreement with this opinion, suggesting that the damage of waiting may be greater than the benefit that could be achieved in patients who lose less weight and experience exacerbation of their co-morbidities. Inge and Xanthakos (240) urged caution around using VSG in very young people and concluded that "there is good reason to believe [it] may be contraindicated" in growing children. They rightly highlight possible physiological consequences of gastrectomy that might influence normal growth and bone development in pre pubertal children. However, the same team stated that this is a research area with many unanswered questions. Disagreement exists surrounding the effects of obesity itself on bone development. Several authors have reported advanced bone age and mineral density in obese young people (241). Al Qahtani suggested that, as paediatric obesity is increasing in prevalence and severity, the increasing problem of super obesity in youth now requires the attention of all paediatric health-care providers, along

with cautious study of all rational interventions at the societal as well as individual level. In this regard, accumulating evidence proposes that young people who are currently undergoing bariatric surgery should expect significant improvements in obesity status and associated comorbidities. It is also promising that improvements in health and psychosocial wellbeing may go beyond course of these young people with extreme obesity, after co-morbidities could be expected that which would be anticipated if weight loss surgery were postponed until later in the life course of these young people with extreme obesity, after co-morbidities could be expected to have progressed. Following increasing numbers of reports of positive outcomes in both medical literature and an increasing overall acceptance in the global media, it seems likely that greater numbers of young people will pursue surgical interventions for obesity in the future (198).

1.5 Mechanisms of weight loss following bariatric surgery: lessons learned from RYGB

The Roux-en-Y gastric bypass (RYGB) includes a small gastric pouch (15-30 mL) on the lesser gastric curvature (242;243), which is completely divided from the gastric remnant and then anastomosed to the jejunum (leaving an alimentary or Roux limb of typically 70-100 cm). The size of the gastro-jejunal anastomosis is controversial as initially it was thought that an element of restriction may be helpful in slowing the progress of food from the esophagus into the jejunum, but more recently the aim has been rapid transit of food into the jejunum to generate the gut signals to reduce meal size (244). Bowel continuity is restored by an entero-enteral anastomosis between the excluded biliopancreatic limb (BPL) and the alimentary limb. This anastomosis is usually performed 70-100 cm distal to the gastro-jejunostomy, although it has also been performed up to 250 cm distally in an attempt to induce calorie malabsorption (242). Recognising the potential of operations such as the biliopancreatic diversion or mini-gastric bypass to employ a longer BPL and achieve greater reduction in insulin resistance, renewed interest has emerged surrounding in the length of the biliopancreatic limb BPL (245). Operative times vary from around 45 to over 120 minutes depending on the specific

technique and surgeon, and the average hospital stay is usually 1 to 3 days, although successful same-day discharge following RYGB procedure has been reported (246). Early complications, within 30 days after surgery, occur in approximately 4% of patients and include bleeding, anastomotic leakage and visceral perforation, each of which may require surgical re-intervention (195). Late complications, such as significant abdominal pain, small bowel obstruction, anastomotic stenosis or marginal ulceration, can occur in 15-20% of patients from 30 days after surgery onward and surgery or endoscopic treatment are often used both for diagnosis and treatment (247). Even though RYGB does not address some of the aetiological factors of morbid obesity, such as the obesogenic environment we live in, it does successfully achieve 20-30% weight loss and maintenance across 2 years or more (248-250). It also offers improvement or remission of much obesity-related comorbidity (251-255), such as hypertension, T2DM, obstructive sleep apnoea (OSA), and musculoskeletal pain. Approximately 40% of obese patients with T2DM go into remission within days or weeks after RYGB (256). RYGB is the most extensively studied procedure regarding underlying weight loss mechanisms. Below is a description of the mechanisms through which RYGB surgery enables weight loss for obese patients, which helps in understanding its complications following studies in both humans and animal.

1.5.1 Food intake

1.5.1.1 Research studies

Hunger and fullness

Lifestyle changes involving a lower calorie diet can be effective at initiating weight loss. However, most of the results from randomized controlled trials (RCT) are disappointing regarding long term weight loss maintenance (257;258). Approximately 70-80% of patients fail to maintain their initial lifestyle-induced weight loss and this is thought to be due to physiological compensatory responses that defend the previous weight “set point” (259). Whilst on a long-term low-calorie diet, patients usually report an increase in hunger, a decrease in satiety and pre-occupation with energy-dense

fatty and sweet food (260;261). This may be part of a normal physiological response, rather than being due to lack of motivation. Reduced calorie intake after RYGB is usually a consequence of significantly smaller meal sizes, and reduced calorie content of food eaten (262), compensated only partially by increased meal frequency (263). Enhanced satiety is the dominant contributing factor (264). A dramatic decrease in daily energy intake, to around 600-700 Kcal (262;265), during the first month post-surgery is followed by an increase in intake to 1000-1800 Kcal over the first year (262;266-272). An average reduction of 1800 kcal per day from pre-operative intake can be sustained for several years (272;273). Protein intake during the first year after surgery is often lower than recommended, at 0.5g/kg, rather than the recommendation of at least 1.5gm/kg/day (274;275). The mechanisms are unclear, but this may be due to a temporary intolerance of higher protein diet and dairy foods (262;265;267;276-278). The relative intake of fat and carbohydrates decreases during the first year post-surgery, but returns to baseline levels after one year (262), although the contribution of high and low glycaemic index carbohydrates may change. Many patients reduce their intake of high glycaemic index carbohydrates and increase their intake of lower glycaemic index carbohydrates. Changes in behaviour associated with eating after RYGB were reported in the 1970s using structured interviews, which suggested that patients reached satiety more quickly, the most common reason given as a “lack of desire” for food (279).

1.5.2 Potential Mediators

1.5.2.1 Increased transit of food into the mid gut through the gastric pouch

Whether the size of the gastric pouch and stoma in RYGB surgery affects food intake and body weight is contested. It remains controversial in both the human and animal literature whether a larger gastric pouch and stoma causes less weight loss (280;281;281-284). The stoma may initially cause food to be “stored” in the pouch and not empty rapidly enough, but appears to become more “compliant” with time, allowing food to transit more easily from the pouch into the alimentary limb. Thus, the initial diameter of the anastomosis may not affect weight loss in the long term (285). To

study the effects of RYGB stoma size, a high pressure manometer was used, which showed that a large stoma with a small pouch was associated with a lower pressure in the pouch (immediately proximal to the gastrojejunal anastomosis) compared with the alimentary limb (286). This suggests there was no restriction at the level of the stoma, because of the absence of a high-pressure zone proximal to the pouch. Insertion of a gastric balloon into the alimentary limb and inflation of the balloon to a pressure of 20 cm water demonstrated that patients with the highest pressure generated by the alimentary limb had the smallest meal volume during an *ad libitum* meal. In contrast, those with the lowest pressure in the alimentary limb took longer to terminate their meal. Mechanoreceptors within the alimentary limb may be important determinants of meal size if food rapidly transits through the pouch to reach the alimentary limb in a less digested state than usual. The component that determines caloric intake may be the alimentary limb and not the pouch size or stoma diameter.

1.5.2.2 Hormonal

RYGB alters endogenous gut hormone responses to a meal. Glucagon like peptide-1 (GLP-1), peptide YY (PYY), and ghrelin have been the best studied candidates in the context of reduced food intake and sustained weight loss after RYGB. GLP-1 and PYY responses to mixed meals or oral glucose have been at the centre of interest of several studies investigating patients six weeks to 10 years after RYGB (287-292). Significantly elevated responses are seen in GLP-1 and PYY as early as 2 days after RYGB (293) and may remain elevated for more than a decade after RYGB (294). Patients who lost the most weight after RYGB also had the highest levels of these postprandial satiety gut hormones (295;296). Blocking the release of these hormones in humans and rats with octreotide increased food intake after RYGB, but not after adjustable gastric banding (AGB) surgery in humans (292) or sham operations in rats (297). Mechanistic studies in rodents have suggested the physiological significance of PYY, because weight loss in PYY-knockout mice after a RYGB variant was lower than in wild-type mice (298). Exogenous PYY specific antibodies also increased food intake in rats after bypass type

procedures (292). Physiologically, PYY has been shown to delay gut transit time, but probably does not increase energy expenditure in human (299). GLP-1 responses are very similar to those of PYY after RYGB, but have additionally been linked with increases in insulin secretion (300;301). Postprandial responses of GLP-1 before surgery do not correlate with change in weight loss after surgery, suggesting that pre-operative gut hormone responses are not prognostic (302). Enhanced GLP-1 signaling on its own is also not sufficient to reduce body weight after RYGB suggesting that it is multiple gut hormone responses that mediate the increased satiation after a meal (303). Reduced ghrelin was the first proposed hormonal mechanism to explain weight loss after RYGB. At first ghrelin levels were thought to be lower compared to diet-induced weight loss, which increased ghrelin in a control group subjects (304). It was postulated that this decrease was partially responsible for reduced hunger after RYGB. Subsequent studies in patients after RYGB were more controversial, reporting a reduction in fasting and postprandial ghrelin levels (291;305-311), no alteration in fasting and postprandial levels (292;293;312-320), and a rise in fasting ghrelin levels (321-325). Considering all the data and variability, it is likely that RYGB results in a comparative ghrelin deficiency considering that ghrelin normally increases after diet-induced weight loss, but the magnitude of this contribution is unclear (326;327).

1.5.2.3 Neural

The vagal afferent fibers in the gastric and proximal small bowel mucosa are known to be sensitive to mechanical stretch in order to detect the volume of ingested food (328). The vagus nerve, with both the ventral and dorsal gastric branches on the large gastric remnant, is transected during the formation of the gastric pouch. The vagal fibers to the gastric pouch are thus intact and these could mediate satiety as food passes through the pouch. The vagal denervation more distally may attenuate signaling. Taken together, this may play a role in satiation (329). Visceral sensory information from the gut is communicated centrally using the afferent (sensory) vagus nerve signaling to the nucleus of the tractus solitarius (NTS). Here, visceral sensory information, hormonal

and metabolic inputs are integrated together with neuronal inputs from other brainstem areas (330) and may well be the most important way in which RYGB signals to the brain. Transmission of these signals involving gut hormones, such as ghrelin, may be impaired after vagotomy (331). RYGB appears to have the potential to alter neural responses (332) to reduce hedonic behaviour associated with eating highly palatable and calorie dense foods. These changes in reward value of food may alter the amount of food consumed (279;333-335).

1.5.2.4 Change in bile acids

Bile acids are agonists for the cell-membrane G protein-coupled receptors, TGR5, which in turn enhance the release of GLP-1 and PYY. Bile acids also bind the farnesoid X receptor (FXR) (336). The anatomical changes after RYGB result in bile progressing down the biliopancreatic limb to the distal L cells without mixing with food. As a result the availability of undiluted bile acids in the distal intestine may enhance stimulation of TGR5 receptors on L cells (337). Serum bile acid concentration is raised after RYGB (338) and is associated with increased energy expenditure possibly through signaling via the cyclic adenosine monophosphate cAMP-dependent thyroid hormone triggering enzyme type 2 iodothyronine deiodinase (339). Fibroblast growth factor (FGF) 19 is increased and binds to Fibroblast Growth Factor Receptor (FGFR4), activating fibroblast growth factor Receptor c-kit (FGRR1c) in the presence of co-receptor β Klotho (340). The result is increased protein synthesis in the liver (341). FGF19 also plays a role in enhanced mitochondria activity (341). Activation of the FXR receptor may facilitate the effects of bile acids on energy homeostasis through FGF19, which is released from ileal enterocytes and can lead to an increase in metabolic rate and a decrease in adiposity (342;343). Bile acids, after a mixed test meal in human subjects, correlated positively with circulating GLP-1 and PYY, but negatively with ghrelin (344). Pournaras et al. demonstrated that total plasma bile acids are elevated after RYGB (345) and suggested that they may be partly responsible for the intestinal hypertrophy, anorexigenic hormone secretion and alterations in gut microbiota (346).

1.5.2.5 Change in gut microbiota

Obesity is associated with low-grade inflammation, increased Firmicutes and decreased Bacteroidetes in animals (347), and humans (348-350). The intestinal microbiota has also been shown to utilise energy from food and thus increase the host's energy-harvesting capacity (351). Proteobacteria have been shown to increase after RYGB in humans (352), with the major contributor being *Enterobacter hormaechei*. The significant improvement of weight, inflammation and metabolic status after surgery was associated with increased bacterial variety. An association was observed between adipose tissue gene expression and bacterial genes at baseline with a 10-fold increase three months after surgery, and this may suggest a restored cross talk between both the gut microbiota and the host (353). After RYGB, acidity was reduced in the alimentary limb, leading to a decrease of hydrochloric acid flux in the gut, while bile acids were increased in the biliopancreatic limb.

Bacteroidetes growth was attenuated at lower pH, whereas *E. coli* increased at a higher pH. Gut microbiota quickly adapt in a “starvation-like state” created by RYGB and rapidly and sustainably increase. Changes in microbiota in mice after RYGB were independent of weight alteration and caloric restriction (354). Transfer of the gut microbiota from RYGB-treated mice to non-operated, germ-free mice resulted in weight loss and reduced fat mass in the recipient animal. The altered microbial production of short-chain fatty acids that increases may offer a partial explanation (354). Although RYGB did not change gut microbiota from the “obese state” to the “lean state” it did create a “third state” which, on balance, appeared to be associated with many of the beneficial characteristics of RYGB.

1.5.3 Food preferences

1.5.3.1 Observations

Weight gain has been linked to a preference for both sweet and/or high-fat foods (355;356), which may partly explain why obese people regain body weight frequently after “dieting” (357;358). The

common view summarised previously by Pangborn and Simone is: “In the mind of a normal person, sugar and sweets are ‘fattening’ and most overweight people have a ‘sweet tooth’” (359). Hedonism associated with palatable foods is considered a significant factor, which increases the prevalence of obesity. A motivational factor that is referred to as “hedonic hunger” (360) may be a trigger for overeating (361). After RYGB, patients tend to increase the intake of fruit and vegetables, as well as low fat food (362;363). The dumping syndrome was thought to induce these changes in food preference (364), and it is often considered as a useful characteristic of the RYGB to “teach” patients to avoid calorie-dense foods and thus consume fewer calories (365). However, patients after RYGB also appear to make healthier food choices and adopt a more balanced diet, even when they do not experience dumping (362;366), and have considerable reduction in energy intake (EI) and energy density. In a comparison of food groups eaten by a group of patients after RYGB, the total number of servings from fat, grains and sweetened beverages was reduced and remained reduced in the longer term. Meats, dairy products, fruits, and sweets, however, were reduced in the short term, but then returned to baseline by twelve months (262). When energy intake was reduced to 1300 Kcal, 60% and 25% of patients, respectively, were consuming less than one serving per day from both fruits and vegetables. Intake of whole grains increased from 25% to 40% within the first three months, but then returned to baseline at twelve months (262). The association between reduced diet energy density and weight loss is controversial as some studies describe no association (367), while others show shifts in food preferences to be partially responsible for the decreased calorie intake and weight loss after RYGB (368). RYGB in humans appears to alter taste through both unconditional and conditional mechanisms (264;369-371), leading to the concept of “behaviour surgery” (364).

In 1987 Sugerman et. al. reported that “sweet-eaters” did particularly well after RYGB (372;373). Some of the initial findings were confounded by intolerance to sweets related to symptoms of the dumping syndrome (279;372-374). Conditioned taste aversion may thus be a factor in some patients. These initial assumptions resulted in many clinicians thinking that the RYGB works by “punishing” the “poor behaviours” of obese patients. The notion that RYGB becomes an external enforcer that goes

against the free will of the patient has led to some authors questioning the morality of RYGB as a tool that changes patients' behaviour, against patients' natural wishes (375). This misconception may have reduced the wider acceptance of RYGB as a valid physiological treatment for the pathology that results in obesity. Classical *conditioned food aversion* is, however, an unlikely explanation as most patients with severe dumping still report that they enjoy the taste of sweet foods, but that they have learned to consume only small quantities that do not cause negative visceral symptoms, or to consume sweets at night before bedtime, suggesting a *conditioned food avoidance* to be a more likely explanation. Distinguishing between the terms is important, because avoidance implies that the palatability of sweet or fat didn't change when small quantities are consumed, but that the subject "learns" to stop consuming the food sooner (earlier avoidance), because large quantities may have negative visceral consequences (376-378).

1.5.4 Mediators

RYGB could be exerting its effects on food selection and preference through any one of the taste function domains important in normal physiology, such as sensory-discriminative (stimulus identification), hedonic (ingestive motivation) and physiological (digestive preparation) (379;380). Affective responses to taste stimuli, which can be considered an example of ingestive motivation, can be both conditioned and unconditioned. It remains controversial which of these three domains are involved and what their interactions are to determine food preferences after RYGB surgery. For example, RYGB could have effects directly on the central gustatory pathways related with feeding and reward through gut hormonal mediators. Alternatively, changes in the sensory signals could alter the intensity or the quality of tastants, but also lead to an unconditioned change in palatability. If RYGB causes visceral malaise after ingestion of fat, then it is possible that the palatability of fat could alter through a process of learning (conditioned response) (381). Although there are suggestions in animal models that the hedonic properties of sweet and fat stimuli may change after RYGB (263;381-385), less work has been done in humans. Miras et al., using the progressive

ratio task, showed that RYGB resulted in the selective decrease of the reward value of a sweet and fat tastant, but not vegetables (386). Further support comes from studies of brain reward cognitive systems linked to eating behaviour, as studied by functional MRI (fMRI), where brain hedonic responses to calorie-dense food are lower after RYGB compared to patients who have lost similar amounts of weight after adjustable gastric banding (369).

1.5.4.1 Energy expenditure

According to the laws of thermodynamics, energy that enters a system (energy intake) must either be stored (body energy gain) or be used (activity, heat or faecal energy loss). Energy expenditure (EE) is usually decreased during food restriction, a phenomenon known as the “starvation response” (387). Weight loss in rodent models of RYGB is associated with preservation of lean body mass and increased EE (387). Humans demonstrate decreased basal metabolic rate, but increased meal-induced thermogenesis after RYGB (272;363;388-394).

Evidence is now also emerging to suggest that the metabolic rate of the small bowel is increased after RYGB with a greater carbohydrate consumption, which may explain the changes observed in respiratory quotient after these operations (395). Reduced resting energy expenditure (REE) or basal metabolic rate after RYGB (363;388;396-398), may be attenuated due to relative lean mass preservation. Patients who regain the weight they lost two years after RYGB have lower REE (390), suggesting that elevating REE after RYGB may enhance weight loss. Physical activity may further help increase activity-related EE and also preserve lean mass, and therefore REE, after RYGB (399).

1.5.4.2 Calorie malabsorption

Several bariatric operations were designed to result in malabsorption of calories (400). The exclusion of the approximately 10% of the bowel (70-100 cm of BPL) after RYGB is unlikely to result in calorie malabsorption. Moreover, the exaggerated gut hormone responses that reduce gut transit after

RYGB do not alter oro-caecal transit time or functional enterocyte mass (256). RYGB may, however, impair pancreatic exocrine function, which could contribute to a small degree of fat malabsorption, the magnitude of which is probably too small to contribute substantially to weight loss (401-403).

1.6 Mechanisms of complications

The rise in the number of RYGB procedures (404) has also increased the absolute number of complications associated with this procedure, even though the percentage of patients with complications has reduced due to better surgical experience (405). Postprandial hypoglycaemia, even in patients without T2DM, can occur several hours after a meal and is distinct from early dumping syndrome, which occurs within minutes after eating (406;407). Early dumping is a consequence of rapid emptying of food into the jejunum due to the lack of a pylorus presumably causing neural activation in the proximal alimentary limb (408). Late dumping or “postprandial hypoglycaemia” occurs 1-3 hours after ingesting a meal and is a result of the exaggerated insulin response to high glycaemic index carbohydrates in the meal. The proposed mechanisms involve increased β -cell mass, improved β -cell function and non- β -cell mechanisms, which may include a lack of ghrelin (a counter regulatory measure to hypoglycaemia) (304;409). In addition, the sustained weight loss can reduce insulin resistance, which renders the previous insulin responses needed pre surgery to suddenly become excessive. The aetiology of hypoglycaemia is likely to be different for individual patients and is also probably a mixture of the anatomic, hormonal, and metabolic changes after RYGB (410). Although treatment of this complication can be difficult, pancreatectomy is no longer advised (411). Rather, a multimodal medical approach is favored (412).

1.6.1 Unexplained abdominal pain

Up to 10% of the patients complain of unexplained chronic abdominal pain which can be difficult for both the treating clinician and patient to acknowledge (413;414). Mild abdominal pain is reported by

up to 95% of patients at some point after RYGB (413;415-417). Symptom severity fluctuates between vague discomfort to severe colicky pain (418). Vomiting and nausea, especially if prolonged, are symptoms of pathology and are not part of the normal postoperative course after RYGB, yet some reports suggests up to 80% of patients report the symptoms at some point after surgery (413;415). Abdominal pain may be recurrent and it should be remembered that internal hernias may spontaneously reduce, causing pain to be intermittent. Early investigation of acute symptoms of abdominal pain is mandatory at first presentation due to the risk of obstruction, volvulus and ischaemia of the herniated bowel (413;419). Cross-sectional imaging is often unhelpful and the use of laparoscopy is frequently required for diagnosis. Management protocols for chronic unexplained abdominal pain are not clearly defined, but the jejunal-jejunal anastomosis is currently receiving more attention as a possible cause for these chronic problems.

1.6.2 Anastomotic stenosis

When the circular stapler technique is used, anastomotic stenosis can be a common complication, with a reported incidence of up to 27% and a recurrence rate of up to 33% (142;420). If dysphagia occurs, it is usually within 6 months of surgery. Endoscopy can often be used both as a diagnostic and an interventional tool.

1.6.3 Vitamin deficiencies: iron, vitamin B12, folic acid, vitamin D, and calcium

Iron deficiency occurs in up to 49% of patients after RYGB (421). Reduced acid production in the stomach pouch decreases iron absorption (422). For iron to be absorbed, the ferric iron in foods has to be reduced to the ferrous state, but because the volume of hydrochloric acid produced is lower after RYGB, this process is attenuated (423). Reduced intake of iron-rich foods after RYGB such as red meat may also contribute (424;425). In the stomach, both pepsin and hydrochloric acid are required for absorption of vitamin B₁₂. Deficiencies of vitamin B₁₂ occur in up to 70% of patients after RYGB (425-427) because of achlorhydria, reduced vitamin B₁₂ absorption from foods and reduced ingestion

of meat, and insufficient secretion of intrinsic factor after surgery (423). Folic acid deficiency affects up to 35% of patients after RYGB. The proximal third of the small bowel is most important in folate absorption, which is reliant upon hydrochloric acid (427). Vitamin B₁₂ also acts as a coenzyme in the conversion of methyltetrahydrofolate to tetrahydrofolate. Thus, folate deficiency might result from achlorhydria, bypassing of the proximal small bowel, vitamin B₁₂ deficiency and/or decreased folate ingestion (425-428). Hypocalcaemia occurs in up to 10% and low serum 25-hydroxy vitamin D levels in up to half of RYGB patients (429). Nevertheless, a study has shown most patients with obesity had significantly lower basal 25-hydroxyvitamin D concentrations and higher parathyroid hormone concentrations as compared to age-matched lean controls (430). Deficiencies may occur because calcium is typically absorbed in the proximal small bowel, which is bypassed after RYGB. Intolerances can also develop to important calcium-rich dietary sources, such as milk, especially if the fat content is high. Calcium can be released from bone, as is evident from an increased bone turnover and subsequent reduced bone mass after RYGB (431;432). The higher bone turnover in the RYGB patients could be partly due to weight loss in these patients (433), but animal studies suggest that bone loss exceeds that which would be expected from weight loss alone (434).

1.6.4 Loss of bone density

Many patients with obesity have a higher than normal bone density before surgery, due to long-term excessive weight bearing. This may be protective and partly explains the question of why the loss of bone density after RYGB does not cause more bone fractures (435;436). Multiple mechanisms may contribute to RYGB reducing bone density, including physiologically reduced mechanical load related to weight loss after surgery, hyperparathyroidism due to insufficient calcium consumption, or reduced intestinal calcium and vitamin D absorption. Humoral factors from adipose tissue (oestradiol, leptin, adiponectin), pancreas (e.g., insulin, amylin), or the gut (ghrelin, glucagon-like peptide-2, glucose-dependent insulintropic peptide) may also play a role (437;438), by connecting a web of consistent regulatory pathways (437).

1.6.5 Kidney stones

Hyperoxaluria is common after RYGB, but the incidence of renal calculi is much lower than after jejunal-ileal bypass (JIB) (439-441). Comparison with the JIB is important, because the incidence, as well as the potential mechanisms, may be different after RYGB. The lithogenic effects after RYGB may stem from reduced calcium binding to oxalate in the intestinal lumen. The excess oxalate is then cleared by the kidneys resulting in hyperoxaluria and calcium oxalate nephrolithiasis. Five years after JIB, which causes significant malabsorption, almost 21% of patients developed kidney stones (442), but the incidence of kidney stones after RYGB appears to depend on a combination of other factors, such as hydration status and urine volume (441). Patients in high stone-forming areas of the world demonstrate an increased susceptibility to stones while those in low stone-forming countries may have an incidence similar to the background population (443). Thus RYGB alone is not enough to cause kidney stones, but it does potentiate other predisposing factors.

1.7 Mechanism for weight loss post bariatric surgery: VSG vs. RYGB

1.7.1 Food intake and underlying mechanisms

Lifestyle changes with a low-calorie diet can be effective at initiating weight loss. However, most of the results from randomized controlled trials (RCT) are disappointing regarding long term weight loss maintenance (257;258). Approximately 70-80% of patients fail to maintain their initial weight loss thought to be due to physiologically compensatory responses that defend the previous weight “set point” (259). Whilst on a low-calorie diet, patients usually report an increase in hunger, a decrease in satiety and a pre-occupation with energy-dense fatty and sweet food (260;261). This may be part of a normal physiological response and not due to lack of motivation.

Reduced calorie intake after bariatric surgery, such as VSG and RYGB, is usually a consequence of significantly reduced meal size, compensated only partially by increased meal frequency (263), with increased satiety being the dominant contributing factor (264). Changes in behaviour associated with eating after RYGB were reported in the 1970s using structured interviews. These suggested that patients reached satiety more quickly than when compared to before RYGB, with the commonest reason given as a “lack of desire” (279).

1.7.1.1 Hypothalamic signaling

The expression of AgRP, which works by increasing appetite and decreasing metabolism and energy expenditure, remained unchanged in rats undergoing VSG (444). This finding might suggest that the rats with calorie restriction were hungry and the VSG rats were not. However, in the same experiment, there was no change in the expression of pro-opiomelanocortin or neuropeptide Y following VSG. There is little evidence to suggest that VSG or RYGB decrease the weight ‘set point’ by changing the expression of key signaling elements in the hypothalamic nuclei (264).

1.7.1.2 Hormones

RYGB and VSG might change the signals from the gut to the hypothalamus and brainstem. The postprandial release of the anorexigenic hormone peptide YY (PYY) is increased after both VSG and RYGB, but not after AGB or caloric restriction (260;290;292;314). Glucagon-like peptide-1 (GLP-1) responses are comparable to those of PYY after both VSG and RYGB (301). GLP-1 is secreted by the L-cells of the small bowel, together with PYY, with higher concentrations in the distal ileum and colon(445). Whether GLP-1 is essential for VSG-induced weight loss has been questioned, as the procedure was similarly effective in both GLP-1 receptor wild-type and knockout mice (446). The rapid delivery of nutrients to the distal ileum following RYGB may be responsible for the exaggerated increase of both PYY and GLP-1 levels (447). In the absence of a ‘shortened’ small bowel in VSG, the rise in levels of these gut hormones has been credited to the rapid gastric emptying (448). It is likely

that the proximal small bowel, upon sensing the arrival of nutrients, is able to signal to the distal small bowel to release gut hormones as well (449). GLP-1 and PYY responses to mixed meals or oral glucose have been at the center of interest of several studies investigating patients, six weeks to 10 years after RYGB (287-292). Significantly elevated responses are seen as early as 2 days after RYGB (293) and may remain elevated for more than a decade after RYGB (294). Patients who lost the most weight after RYGB also had the highest levels of postprandial satiety gut hormones (295;296). Blocking the release of the postprandial satiety gut hormones in humans and rats with octreotide increased food intake in rats and patients with RYGB, but not in patients after AGB surgery (292) or rats with sham operations (450). Ghrelin levels are reduced after eating, with carbohydrates causing a more rapid suppressive effect than protein and lipids (451). Ghrelin levels are reduced after VSG (452) and increased after AGB (453), while after RYGB they may be either decreased, increased or remain unchanged (304;454). It is not clear whether ghrelin is the key physiological player in VSG, as the procedure is similarly effective in ghrelin-deficient and ghrelin-intact mice (455), both surgical and nonsurgical caloric restriction cause fat mass loss and reductions in plasma leptin levels (260;316). The expression of leptin receptors was equally reduced after VSG surgery or pair-feeding and, therefore, surgery does not appear to have a greater effect on central leptin sensitivity (444). There is a considerable amount of data to suggest that both GLP-1 and PYY are significant mediators of weight loss after RYGB, although the evidence is less developed for VSG. PYY acts to reduce food intake and, therefore, maintain weight loss (456). GLP-1 acts to reduce food intake, increase glucose stimulated insulin secretion, improve insulin sensitivity, and may preserve islet integrity (457).

1.7.1.3 Vagal signalling

The contribution of the vagus nerve to weight loss after VSG and RYGB has not been sufficiently explored so far (264).

1.7.2 Mechanical factors

Controversy exists as to whether the gastric sleeve volume in VSG and the size of the gastric pouch and stoma in RYGB surgery affect food intake and body weight (264). Some studies have shown that the larger the gastric pouch and stoma diameter the less weight is lost, both in human and animal models (280-282). Others, however, have not shown correlation between the two variables (281;283;284). Equally conflicting results have been found concerning the volume of the gastric sleeve after VSG (211;458-460). The various methods used to measure gastric volume, patient characteristics and other notable confounders, along with the unclear association between gastric volume and weight loss suggest that the physiological role of this factor might be minimal. Gastric emptying and intestinal transit actually seem to be faster after VSG (448;461-463), which go some way to explaining why the release of anorexigenic gut hormones post VSG is comparable in magnitude to RYGB (264).

1.7.2.1 Caloric malabsorption

An 8%, statistically insignificant increase in faecal caloric density has been established in animal models of VSG (464), but no studies have measured it post VSG in humans. Therefore, the contribution of caloric malabsorption to weight loss post VSG and RYGB appears to be minimal (264).

1.8 Food preferences in obese

High dense food; sweets and fats

Studies have indicated that feeding laboratory animals a variety of calorie dense foods, high in fat and sugar, in addition to their standard chow will induce overeating and obesity (465). The palatability of fat and sugar rich foods may be responsible for a preference for, and the over consumption of certain foods, i.e. the hedonic response to their flavour (466;467). Human obesity

and weight gain have been linked to an elevated preference for both sweet and/or high-fat diet (355;356). The increased appetite for sweet or high-fat foods may explain why obese people gain and regain body weight frequently (357;358). For example, these two energy rich components account for around 60% of the daily energy content of the typical American diet (22% from sugar and 37% from fats) (468). There is a discrepancy between the published studies that have investigated whether people with obesity have a higher preference for sweet-tasting foods, or have a different threshold for sweetness compared to the non-obese (469-478). The common view about sweetness and obesity was summarized by Pangborn and Simone as: 'In the mind of a normal person, sugar and sweets are 'fattening' and most overweight people have a 'sweet tooth' (359). Some individuals show a continuous increase in taste satisfaction as sweetness concentration was raised (i.e. the sweeter the better), while in others, satisfaction increases to a maximum level and then decreased again as sweetness became overpowering (479). In a third group, the satisfaction decreased with increasing sweetness (480). However, the original conclusion of Pangborn and Simone was supported by the majority of evidence from the literature, which suggests that body weight has nothing to do with the perception of, and preference for, sweetness (470;472;473;476;481-483). Neither threshold (473;474;483), nor suprathreshold was different (474-476;482-484) when linked to body weight as well. (2) Higher BMI is linked to a lower perceived sweetness. Therefore, it is necessary to correct comparisons of 'liking for sweet' to account for perceived sweetness. Plotting the liking as a function of sweetness shows that sweet liking is greater among individuals with obesity. This is done by scaling the sweet taste and liking with the gLMS. (3) A lower perception of sweetness is linked with a greater difference between an individual's likings of fat foods compared to liking sweet foods. Bartoshuk and colleagues argued in their review, most of the literature describing those with obesity experiencing less sweetness than those without obesity is compromised by the psychophysical errors described above. The expression of taste loss in patients with obesity may provide researchers with new ways to think concerning liking for sweet and fat tastes in the obese population, with the research team concluding that liking of both sweet and fat tastes increase as BMI increases (471).

This assumption that body weight has no influence of preference for sweetness has prevailed for almost 50 years, justifying the failure of the earlier studies to find sensory or hedonic differences (475), but new data has suggested that there are sensory differences related to body mass index (BMI), challenging the previous assumption (471). It was found that people with a higher BMI tend to find candy less sweet. This novel finding is a result of the use of the general labeled magnitude scale (gLMS) within certain studies, discussed in more detail later herein. Elsewhere, data have shown that obese people tend to favour sugar more than underweight individuals do. Multiple regression analysis demonstrated that individuals with a higher BMI liked sugar more than those with a lower BMI (471). It also demonstrated that this liking increases as a function of sweetness as BMI increases and, as a result, liking increases as BMI increases for the same perceived sweetness. Moskowitz suggested that studying and analysing the liking of sweet tastes in the conditions of the perceived intensity of sweetness is helpful for learning more about obesity (485). The common view regarding fat is comparable to that for sugar; it is presumed that people with obesity show greater liking for high-fat foods. Though, contrary to the evidence relating to sugar, studies on preference and obesity support this general view (357;486;487). In these studies, mixing fat with other dietary components was of special interest for researchers. Drewnowski and his colleagues conducted a study that used dairy products with diverse sugar and fat content to study more about this mixture between fat and sugar and how palatable it is. Data have shown that women with obesity preferred a higher ratio of fat to sweet, and that a mixture of sweet and fat establishes palatability (357). Moreover, an assessment of food preferences found that obese women tend to prefer sweet–fat foods, while obese men tend to favour savoury–fat foods (488). It's not clear yet, why this liking for sweet and fat increases as BMI increases. The relationship between orosensory experience and post-ingestive effects of sweet and fat foods contributes to liking (489), and, indeed, that the hedonism associated with foods is considered a significant factor in the increased prevalence of obesity. In addition, a substantial body of literature has verified the differences in reward behaviours and neural reward functions between obese and lean animals and humans (361;384;490-501). It has not been shown,

however, whether such differences exist before the development of obesity, and are causative, or are a result of obese condition (502). There is much to be learned about the relationship between liking and consuming foods in the near future (471).

1.8.1 Low glycaemic index carbohydrates, including fruits and vegetables

Many researchers have examined the effects of macronutrient measures on satiety, food intake and body weight. Fruit and vegetables are usually considered together as they are often associated in dietary advice, for example “eat more fruit and vegetables”. Even though they may vary greatly in their sensory and nutritional profiles, both are low in fat and high in both fiber and water, which makes them low in energy density (kcal/gram). These properties could be beneficial for weight management by virtue of a contribution to increased satiety and reduced food intake. By adding fruit and vegetables to the diet, overall energy density will be reduced and the quantity of food that can therefore be consumed within a given calorie limit will be greater (503). Satiety is considered by measuring consumption when foods are freely available. Energy density effect satiety i.e. lower energy density equates to enhanced satiety (504-508), and that the amount and type of carbohydrates in fruits and vegetables might also effect satiety and therefore food intake (509). Carbohydrates, when digested, are converted to glucose, and the rate of this conversion process can be determined by measuring plasma glucose concentrations over time (i.e., the glycaemic response). The glycaemic response across two hours after ingesting a portion of food that contains 50g carbohydrate is used to analyse the food by creating an “index”. High glycaemic index (GI) food causes a quick but short-lived rise in blood glucose levels, whereas low GI food causes a slower, more sustained rise (503). Satiety is proposed to be greater in foods with a low GI than those with a high GI, although a strong relationship between GI and satiety, food intake, or body weight has not been established (510;511).

1.9 Determinants of food preferences

Social, cultural and genetic factors contribute to the development, preservation and alteration of dietary patterns and food preferences, taste, and food choices (512;513). Interpersonal relationships, such as family and friendship groups, influence eating behaviour and exert direct or indirect social influences (e.g. beliefs, cooking traditions, food rules that a family may teach their children). Taste and other sensory properties of foods (e.g. smell and texture) are partly responsible for the selection of one food over another. In addition, the hedonic value of food is strongly linked to the functional taste domain, which may be a driving force behind food consumption (514).

1.9.1 The taste system

Taste detection thresholds are only one basic aspect of taste function in general and have been shown to vary as a function of genetics, pharmacological treatment, and neural manipulations (515). The concepts of taste hedonics and alterations in reward responses have not been fully explored as a potential mechanism for the development of obesity. The search for the neural basis of any behavioural or sensory process must begin with a clear articulation of the principles of function. With this in mind, there is ample evidence that the sense of taste serves several functions that can be experimentally classified into at least three general domains (379).

1.9.1.1 Stimulus identification

Stimulus identification is the detection or discrimination of sensory signals arising from taste cell activation in the oral cavity. Stimulus identification involves the discrimination between the sensory signals representing different taste stimuli arising from the interactions of chemical compounds with taste receptors.

1.9.1.2 Ingestive motivation

Ingestive motivation refers to processes that promote or discourage ingestion of foods and fluids on the basis of taste input. Ingestive motivation can be further divided into two functional subclasses: Appetitive behaviour (“wanting”) can be defined as actions that lead to contact with the taste stimulus (e.g. searching, foraging, and approach to a drinking spout) and reflects how much the stimulus is wanted. Consummatory behaviour (“liking”) represents the behaviour that is elicited during the contact with the taste stimulus (e.g. oral motor responses, swallowing) and reflects how much the stimulus is liked.

1.9.1.3 Digestive preparation

Digestive preparation refers to physiological reflexes that fall into a general class referred to as cephalic phase responses, which are internal physiological events triggered by stimulus contact with any sensory receptor of the head (516). Cephalic phase responses generally prepare to digest, absorb and then store nutrients that enter the body through feeding. Cephalic phase reflexes can be both intrinsic and learned. For example, most animals readily learn to avoid foods that render them ill through conditioned taste preferences and conditioned taste aversions, and rats can be conditioned to react aversively to sweet solutions by actively rendering them ill after ingestion. Consequently, they will decrease their intake of the sweet solutions when they are exposed to them again. The vagus nerve is thought to be an important pathway for cephalic phase responses (517).

For taste function assessment, it is important to circumvent the influence of post-ingestive factors in both animals and humans. Post-ingestive effects can be positive (e.g. satiation, fullness) or negative (nausea, visceral pain) and occur after food ingestion. They also include post-absorptive effects. Hence, two important methodological features must be considered for the experimental protocols: First, only small volumes of taste solutions must be used. Second, immediate responses to the taste stimulus should be measured. For animal experiments, the application of these

methodological features requires the use of a special stimulus delivery system and a lickometer (515).

1.10 Food preferences post bariatric surgery

Changes in appetite behaviour after obesity surgery were reported in the 1970s. Halmi in a study conducted earlier, using structured interviews reported that post gastric bypass patients reached satiety much faster compared to before surgery and the reason for reduced food intake was lack of “desire”(279). More importantly there was a statistically significant reduction in the intake for high fat meats and high calorie carbohydrates six months after surgery. At the same time patients found these foods “no longer enjoyable”. In an attempt to explain the changes in high calorie carbohydrate eating, dumping syndrome was implicated, although it was not evaluated further (279). These findings were simulated by Brown (518), who used food diaries to show that both total fat and carbohydrate intake was significantly lower after gastric bypass. Patients stated that they were “not interested in sweets or deserts after surgery”, although again this was not officially quantified. Kenler was the first to conduct a study comparing gastric bypass and horizontal gastroplasty, recognising very early that the superior weight loss after gastric bypass may be due to changes in taste preference rather than gastric restriction (368). This study showed, using diet interviews, that gastric bypass patients consumed 45% less solid sweets, sweet high-calorie beverages, and 37% less milk or ice cream, compared to gastroplasty patients (368). Milk and ice cream consumption increased post-operatively in the gastroplasty group as these food substances were easier to swallow. Dumping syndrome was suggested (but not proven) to be accountable for the changes in sweet consumption (368;519). Some patients reported “losing their taste” for milk and ice cream even without having unpleasant gastrointestinal symptoms. On this basis the authors recommended gastric bypass as a more suitable procedure for sweet and ice cream eaters supporting the findings and recommendations of the Sugerman group (373). Olbers et al. compared patients post RYGB

and vertical banded gastroplasty in the only such randomised controlled trial. After surgery the gastroplasty group consumed a significantly higher proportion of their total calories as fat and carbohydrates in contrast to the RYGB group. Interestingly, gastric bypass led to patients preferring fruit and vegetables and intentionally avoiding fat, in fact reporting feeling unwell after fat consumption, potentially as a result of a dumping phenomenon (363). Furthermore, findings from Le Roux's et al. suggest that changes in fat preference may contribute to long-term maintained weight loss after RYGB (383). In addition, a trend was seen toward greater rates of healthy food consumption on a daily basis and significantly better food tolerance a year after VSG (520). Leahey et al. found that bariatric surgery was connected with major reductions in food cravings and consumption of craved foods, with the exclusion of high-fat foods. Despite these decreases, patients' cravings did not fully reduce to "normative" levels and are not associated with post-operative weight loss (521). Generally, patients' behaviours have a considerable effect on post-operative outcomes after bariatric surgery (522). Based on these findings and the terminology used in the literature of the time (desire, not interested, or intolerance) it became clear that obesity surgery, and specifically gastric bypass, does not just reduce the amount that people eat but also alters the perception of food and possibly eating behaviour. This healthy shift away from high calorie fat and sugar foods to increased consumption of fruit and vegetables could be explained by alterations in the sense of taste.

1.10.1 Changes in taste post bariatric surgery

Bariatric surgery could be exerting its effects on food selection and preference through any one, or a combination, of several functional domains: sensory-discriminative (or stimulus identification), hedonic (or ingestive motivation) and physiological (or digestive preparation) (379;380). Altered taste function in humans can be measured through various means. For example, taste thresholds can be assessed by a variety of objective techniques to measure detection thresholds to sucrose (381;523), urea (524), and hydrochloric acid (524). Taste threshold measurements, however, do not always predict perceived intensity at suprathreshold concentrations (525). The only way to measure

suprathreshold sensitivity is through the use of scaling procedures, in which subjects are asked to rate the intensity of their sensations. This is usually done using visual analogue scales (VAS) that are relatively easy, efficient, and inexpensive. The drawback of VAS in adolescents with morbid obesity is that the patient may indicate a result they think the healthcare professional or researcher would like to elicit. Thus, underreporting or misreporting may be a major confounder, just as in the case of food diaries (526;527).

1.10.1.1 Sensory Domain

Direct measures of behaviour can be used to study the effects of gastric bypass surgery on the sensory domain of sweet taste in obese patients. A technique incorporating the application of constant stimuli to determine detection thresholds has been used to measure taste sensitivity in animal models (385). After gastric bypass, patients' sucrose detection threshold decreased (523), suggesting that surgery has consequences on the sensory processing of taste signals generated by sucrose (381). In fact, RYGB appears to alter most of the domains involved with taste (364).

1.10.1.2 Reward domain: appetitive behaviour

Although there are suggestions in animal models that the rewarding and aversive properties of sweet and fat stimuli may change after gastric bypass (263;381-385), very little work has been performed in humans to determine whether there are any changes in the hedonic domain of taste function after other weight loss surgeries such as VSG. This question has been addressed using the progressive ratio schedule of reinforcement, an operant task first developed by Hodos 50 years ago (528) for use in animals. During the task, the subject is trained to perform a certain number of responses required to obtain a reinforcer (i.e., reward). After delivery of each reward, the response requirement progressively increases until it is so great, the subject stops responding. This point is defined as the breakpoint. The number of responses completed for the last reward received can be used as a proxy of the reward value of the reinforcer and is a pure assessment of appetitive responsiveness driven by

the stimulus properties of the reinforcer such as its taste. Miras et al. found that gastric bypass surgery (RYGB) resulted in the selective reduction of the reward value of a sweet and fat tastant. This application of the progressive ratio task provided an objective and reliable evaluation of taste-driven motivated behaviour for food stimuli after obesity surgery (386). Anecdotal evidence from clinical observation and evidence in rodents after VSG does suggest a shift in food preferences. Seeley et al. showed VSG in rats reduced intake of dietary fat and shifted preference toward lower caloric-density foods as compared with sham operated rats. Progressive-ratio (PR) and conditioned taste aversion paradigms showed changes after VSG in rats. Finally, food choice was compared between VSG and RYGB operated rats, and concluded that these two anatomically different bariatric procedures lead to comparable changes in food choice (529). In contrast, another study failed to show this shift in food preferences after VSG in rats (464). The trend shows that RYGB in humans leads to changes in food preference and possibly fundamental alterations to taste (264;369-371;530). Questions remain over whether humans show similar changes to rats after VSG and, indeed, to humans after RYGB.

1.10.1.3 Reward Domain: consummatory behaviour

Another objective way to study human feeding behaviour, is taste reactivity, as measured by “the involuntary, minute movements of the face in response to a stimulus” (531). These can be studied to enable an impression of the emotional state of an individual as a consequence of the applied stimulus. Taste reactivity studies using facial expression, which looked at infants, apes, new world monkeys and rats, concluded that there were two major reaction patterns seen: the positive, hedonic reaction - typically to sweet taste - was characterised by lip smacking, tongue protrusion and even a smile, while the negative, aversive reaction – to bitter taste - involved grimacing, retracting of the lips, wrinkling of the nose and retraction of the head away from the food source. Other tastes, such as salt or sour, were found to produce responses with intermediate reactions between those described above (532-536). The use of taste reactivity to study the ingestive motivation,

consummatory behaviour in adult humans has been less well investigated. Previous work has shown that adults do demonstrate facial reactivity, with some promising results (533;535;537;538), although these behaviours may be less accurate as a consequence of socialisation and voluntary or higher control (535;539). Taste reactivity has not been used for the study of consummatory reward in obese adults or adolescents previously. A major limitation to the use of facial reactivity is the difficulty in interpretation of these often small and subtle movements (535). A few studies have used the Facial Action Coding System (FACS) with trained interpreters (540).

However, face recognition software packages have recently been developed, which enable a more objective assessment of facial reactivity and can determine the duration of the facial reaction, providing a better overall feedback on the emotional state of the subject (e.g. FaceReader™). This technology is promising and could be further improved in terms of specificity, sensitivity and adapted to cultural and social facial reactivity differences. Metabolic mechanisms may facilitate the effect of bariatric surgery on taste pathways. It has been shown lately, that high levels of PYY activate brain regions related to food reward, including the ventral striatum, orbitofrontal cortex (OFC) and insular cortex (541). Moreover, GLP-1 receptors have also been isolated in brain reward areas (542). GLP-1 and its receptor have been isolated in taste cells of the taste buds and adjacent intragemmal afferent fibers, respectively, interacting in a paracrine manner (543). Accordingly, if bariatric surgery was to affect taste hedonics, it may do so through increased GLP-1 and PYY availability and input to the taste signal pathways at multiple levels, both proximal and distal. Further studies are needed to explore the effect of bariatric surgery on decreasing sweet and fat reward, thus leading to healthier food choices after surgery, which contribute to long-term maintained weight loss. The consequence of VSG on the complex central reward circuits has not yet been studied. By understanding the mechanisms by which VSG decreases consumption of high calorie fat and sweet foods and alters taste responses, new surgical and non-surgical therapies could be developed that reproduce these processes and so encourage safe and effective weight loss.

1.10.2 Eating behaviour and meal patterns

Little is known about eating behaviour and meal patterns following RYGB and other weight loss procedures. RYGB results in early satiety and a reduction in food intake. Bjorklund suggested that the Roux limb could also be a significant determinant for regulating food intake after RYGB surgery (544), where the thresholds for eliciting distension-induced sensations are strongly and negatively associated with preferred meal size (244). Weight loss surgery, including RYGB, changes the acuity perception of food and thus eating behaviour, leading to the concept of “behaviour surgery” (364). In a study conducted by Furnes et al., eating behaviours were compared between rats that underwent VSG and counterparts that underwent RYGB. They found that the food intake and meal size were reduced after VSG but not gastric bypass, suggesting that the control of food intake was independent of the food reservoir function of the stomach (545). Gastrointestinal function, as well as the behaviour of the individual, might be influenced by the psychosocial factors, such as dietary counseling, individual food preferences and dislikes, food culture, previous experiences of dieting and emotional state (244). It is likely that the changes in gastrointestinal functionality after bariatric surgery are the start of a cognitive process, whereby the individual makes preventive changes in behaviour in order to avoid dumping syndrome (406). The general relationship to food is part of the eating behaviour as well (244). For example, dietary restraint is suggested to have an inconsistent role in the development of obesity (546). Loss of control over food intake and a tendency to overeat in the presence of emotional distress are additional types of eating behaviour, yet little is known about their prevalence after bariatric surgery (547;548). Few studies have considered changes in eating behaviour such as meal size and number of meals, and none has studied the effect of VSG on both elements.

1.10.3 Changes in calorie density of food

Studies have shown that energy intake increases depending on the fat content and energy density of the entire diet (549). Dietary energy density (ED) is the amount of energy (calories) in a particular

weight of food, generally presented as the number of calories per gram of food (kcal/gram) (103). It is likely that fat (9 kcal/g) influences the ED values more than carbohydrate or protein (4 kcal/g) because of its very high-energy content, whereas water containing foods, such as fruit and vegetables do the opposite, owing to their low ED (550). Small changes in ED may have a significant effect on the energy intake (EI), as people have a tendency to eat a constant volume of food (550). Diets considered to be of a high dietary quality are usually low in ED (551). Studies that compared Diets considered to be of a high dietary quality are usually low in ED (551). Studies that compared overweight and obesity, have determined the importance of dietary ED on food intake, concluding that lowering ED can reduce energy intake (EI) (549;552). Moreover, Rolls et al. found that ED affected satiety or the feeling of fullness when the proportions of macronutrients were constant (550). Several studies have revealed that dietary management of obesity depends on establishing a low ED diet (553;554). Furthermore, successful weight maintenance programs have also utilized low ED diets (555;556). Studies have represented bariatric surgery to be the only currently available treatment demonstrating long-term efficacy. Considered to be the gold standard, RYGB achieves not only the excellent weight loss described earlier, but also a high level of eating quality. RYGB influences food selection, subjects tending to increase their intake of fruit and vegetables, as well as low fat food after RYGB (362;363). Previously mentioned factors including taste alteration (364) and the dumping syndrome have been considered “useful” characteristics of RYGB because patients learn to avoid calorie-dense foods and eat less at each meal (365). Ernst et al. and Thomas et al. showed that RYGB resulted in healthier food choices and a more balanced diet than AGB (362;366). In addition, Laurenus et al. stated that besides considerable reduction in EI and large difference in consumed food weight (FW) after RYGB, patients reported decreased dietary ED over 2 years. Although there was no association between the reduction in dietary ED and percentage weight loss, changes in food choice were overall nutritionally beneficial (367). To date, no data exists representing the effect of VSG on ED and EI for patients after surgery. It is not clear whether the observed alteration in perception of food is the result of changes in taste or post-ingestive effects.

Whether VSG can influence physiological circuits like the gustatory system is unclear, especially as behaviour focused anti-obesity interventions have not succeeded. It is also not clear at what level of taste transduction this manipulation take place – the taste bud, the brain or both? These questions have raised the interest of obesity and behaviour researchers over the last two decades and have led to ground breaking clinical and preclinical experimental work.

1.11 Hypothesis

The Hypothesis: VSG changes taste, which changes eating behaviour.

1.12 Aims of study

Aims to test the hypotheses of the study:

AIM 1. To assess changes in eating behaviour and meal patterns following VSG in adolescents

Patients have been studied longitudinally before and after surgery, as well as being compared to a non-surgical control group.

SPECIFIC AIM 1.1. To examine whether vertical sleeve gastrectomy (VSG) alters portion size, meal duration and rate of eating.

SPECIFIC AIM 1.2. To evaluate whether pre-meal hunger, post-meal satiation and maintained satiety in relation to voluntary food ingestion are different before and after surgery.

SPECIFIC AIM 1.3. To examine the diurnal distribution and number of meals, examining 24h recall using food behaviour questionnaires, before and after surgery.

SPECIFIC AIM 1.4. To evaluate changes in eating behaviour and meal patterns pre-surgery and at 12

and 52 weeks post-surgery in adolescents following VSG.

AIM 2. To assess longitudinal changes over 52 weeks in taste detection thresholds for sucrose after VSG in adolescents, as compared to the non-surgical control group.

SPECIFIC AIM 2.1. To evaluate sweet taste detection thresholds pre-surgery and at 12 and 52 weeks in adolescents following VSG.

AIM 3. To assess longitudinal changes in appetitive behaviour after VSG in adolescents, as compared to the non-surgical control group.

SPECIFIC AIM 3.1. To evaluate appetitive behaviour pre-surgery and at 12 and 52 weeks in adolescents following VSG.

AIM 4. To assess longitudinal changes in consummatory behaviour after VSG in adolescents, as compared to the non-surgical control group.

SPECIFIC AIM 4.1. To determine changes in “facial expressions” in adolescents when reacting to tastant stimulants after VSG.

SPECIFIC AIM 4.2. To study and evaluate oromotor reflexes, as related to consummatory behaviour pre-surgery and after 10 days and 12 weeks in adolescents after VSG.

CHAPTER 2

METHODS

2.1 Subjects

2.1.1 Sleeve subjects

Sixty adolescent (aged 12-18 years) Saudi subjects with obesity, scheduled for VSG were selected for the study, consisting of fifteen subjects in each arm. All subjects were treated in the obesity surgery clinic at King Saud University (KSU) in Riyadh city, KSA. Inclusion criteria were: BMI ≥ 40 kg/m² or ≥ 35 kg/m² with obesity related co-morbidities, except for T2DM ($\geq 95\%$ body mass index (BMI) on Centers for Disease Control (CDC) for adolescents), and consent to proceed with VSG surgery. Exclusion criteria included pregnancy, breast-feeding, a diagnosis of T2DM, psychiatric illness, an inability to comprehend and comply with treatment requirements and low levels of zinc. The laparoscopic VSG was carried out using a technique that has been standardized and remained the same since the start of patient enrollment (557). Most observations were conducted approximately 2 weeks before surgery and again 10 days, 12, and 52 weeks after surgery. All patients continued their routine post-surgery hospital visits to the multi-disciplinary obesity surgery clinic including dietary counseling. Sleeve subjects were recruited at the obesity clinic in KCUH when attending their initial appointment with the team. A twenty-minute interview was conducted with each individual to introduce the investigator and discuss the study, giving the patient and parent enough time to ask any questions they had. All subjects or their parents provided written informed consent before the study began, and received reward vouchers at every visit. Studies took place in a Clinical Research Centre (CRC) with a constant room temperature of 21°C for all test sessions. All participants received follow up appointment schedules and received a reminder phone call and text message twenty-four hours before their appointment. The sample size was determined based on similar studies, which had previously shown significant results with 9-15 participants after RYGB (381) within our research team at Imperial College London.

2.1.2 Control subjects

A control group of 40 (10 per study arm) non-surgically-treated Saudi adolescents, was recruited from the siblings of surgical patients and was matched according to gender and age. These individuals represented a broad range of weight categories, from normal weight to obese. Control subjects underwent the same experiment 8-12 weeks apart to validate the study (four arms) sample size according to each arm methods. Exclusion criteria included pregnancy, breast-feeding, a diagnosis of T2DM, psychiatric illness, an inability to comprehend. Control subjects were recruited by calling the parents of surgical subjects, involving the same process of interview, consent and follow-up as surgical patients' thereafter. Studies took place in a Clinical Research Centre (CRC) with a constant room temperature of 21°C for all test sessions. All participants received 2nd appointment schedules and received a reminder phone call and text message twenty-four hours before their appointment. The sample size was determined based on similar studies, which had previously shown significant results with 9-15 participants after RYGB (381) and matching control group within our research team at Imperial College London.

A school campaign to recruit controls was determined in one of the National schools in Riyadh, KSA. It wasn't easy to recruit subjects because it interferes with the school timing. An educational lecture, brochures and flyers were prepared for this purpose but it didn't work. Students and parents were concerned about being absent from school due to the experiment timing.

2.2 Methods (in brief)

2.2.1 Aim 1: Changes in eating behaviour and meal pattern post VSG in adolescents

Ten non-obese control subjects were examined twice, while the 17 obese surgical subjects were examined before surgery and twice (12 weeks and 52 weeks) after VSG. At these times, subjects consumed a standardised ad libitum test meal in the Clinical Research Centre (CRC) in a standardised quiet private room. Meal duration and meal size was measured, as well as pre-meal hunger and post-meal satiation, which was measured twice after the meal. At each study visit, habitual meal patterns were recorded using a standardised validated questionnaire for the analysis of meal frequency, dietary behaviour and temporal distribution over 24 hours.

2.2.2 Aim 2: Sweet taste thresholds changes post VSG in adolescents

Ten non-obese control subjects were examined twice, while the 15 obese surgical subjects were examined before surgery and twice (12 weeks and 52 weeks) after VSG. Seven sucrose concentrations were used in this study: 2.1, 6.25, 12.5, 25, 50, 100 and 300 mM. Concentrations were tested in eight blocks, each block consisting of seven sucrose and seven water stimuli. Sucrose and water stimuli were presented in a random order without replacement. Subjects were given a period of five seconds to sample the stimulus in the mouth and were asked to indicate whether the stimulus was water or not.

2.2.3 Aim 3: Changes in appetitive behaviour post VSG in adolescents

Ten non-obese control subjects were examined twice, while the 21 obese surgical subjects were examined before surgery and twice (12 weeks and 52 weeks) after VSG. The Progressive Ratio Task was performed in this arm with an increasing number of computer mouse clicks needed to earn a sweet. The starting ratio to get a reward was 10 clicks, with a geometric incremental increase by a factor of 2 (i.e., 10, 20, 40, etc.), until the participant stopped responding, which was deemed the breakpoint.

2.2.4 Aim 4: Changes in consummatory behaviour post VSG in adolescents

Within this pilot study, 5 non-obese control subjects were examined twice, while 7 obese sleeve subjects were examined before surgery and twice (10 days and 12 weeks) after VSG. A 50 mL chocolate milkshake flowed directly and securely into the subjects' mouths by hanging the milkshake in a giving set bag from a 1.5-2 meters stand, using gravity to deliver a rate of 25mL/minute. When the record button on the camera was pressed, the infusion started along with the video recording and the investigator left the room for two minutes before the recording stopped.

2.3 Statistics

Parametric or non-parametric tests depending on the distribution of the data were used. All normally distributed data were expressed as mean $\pm$ standard error of the mean (SEM) for demographic data and 95% confidence intervals (CI) for other variables. One-way analysis of variance (ANOVA) with repeated measures and post-hoc Bonferroni tests were used to test for significant differences between pre- and post-operative measures. Two-way analysis of variance (ANOVA) with repeated measures and post-hoc Bonferroni tests were used to study the effect and interaction of Group and Time on different variables. Linear regression models were used to examine associations. Significance was determined as $p < 0.05$. Raw data was analyzed using graphpad Prism® software package or SPSS® v22 or Mypstat® (Systat® 13).

CHAPTER 3

**CHANGES IN EATING BEHAVIOUR AND MEAL
PATTERNS FOLLOWING VERTICAL SLEEVE
GASTRECTOMY IN OBESE ADOLESCENTS**

3.1 Introduction

Childhood obesity is defined as a BMI at, or above, the 97th percentile and is one of the most serious public health and medical problems worldwide, but also specifically in the Gulf area (35). In the Gulf region the usual diet has changed in terms of quantity and quality, with more calories being consumed as fat and high glycemic carbohydrates (39). The overall prevalence of obesity among adults in the Kingdom of Saudi Arabia is 35.6%, with a further 36.9% of patients being overweight (46). The prevalence of overweight and obesity among young people, aged ≤ 20 years old, in Saudi Arabia was estimated at 28%, an estimated 11-23% overweight and 3-25% obese. More than 50% of children in SA between 14 and 18 years had a weight above the 85th percentile (49). Obesity at this age represents one of the most frustrating and difficult diseases to treat even if interventions are started at an early age (58). Frustratingly, an understanding of the mechanisms preventing an obese adolescent or adult from losing weight and maintaining weight loss remains elusive (15).

Social, cultural and genetic factors contribute to the development, preservation and alteration of dietary patterns and food preferences, taste, and food choices (512;513). Interpersonal relationships in family and peer groups influence eating behaviour and exert direct or indirect social influences (e.g. beliefs, cooking traditions and food rules, which a family may teach their children). Taste and other sensory properties of foods (e.g. smell and texture) are partly responsible for the selection of one food over another. The hedonic value of food is strongly linked to the functional taste domain, which may be a driving force behind food consumption (514). Weight-loss maintenance after changes in lifestyle, diet, and exercise have been disappointing (257). Bariatric surgery is a successful intervention for sustained weight-loss and is cost-effective for morbidly obese people compared with non-surgical interventions (558). Although bariatric surgery may not treat the aetiology of morbid obesity, it is able to achieve 25-35% long term weight loss maintenance (559), while also improving many co-morbidities (560), such as disturbed eating behaviour and impaired quality of life (QoL) (561).

Vertical sleeve gastrectomy (VSG) is effective for weight loss over two-years (229;562), though more long term data are awaited. Al Qahtani et al., reported the largest series in the world of VSG in young people, which was performed at King Saud University Hospitals, Riyadh, Saudi Arabia. The reported outcomes of 108 patients aged between 5 and 21 years showed successful short-term weight loss in more than 90% of patients after VSG and resolution of 70% of their co-morbidities within 2 years after surgery. Longer-term data are needed to better understand what happens as these patients mature into adulthood (236). Anecdotal evidence from clinical observation and evidence in rodents after VSG suggest a shift in food preferences. Seeley et al showed VSG in rats reduced intake of dietary fat, and shifted preference toward less calorie-dense foods as compared with sham operated rats. When food choice was compared between VSG- and RYGB-operated rats, comparable results were achieved with these two anatomically different bariatric procedures (529). RYGB in humans may lead to changes in food preference and fundamental alterations to taste (264;369-371). This research wanted to determine whether humans after VSG change their food preferences and eating behaviours. This study aimed to test the hypotheses that there would be changes in meal patterns, attitudes to eating and foods selected by adolescents following VSG. Using a prospective approach, the specific aims were to evaluate (1) portion size, meal duration and rate of eating, (2) attitudes to eating, (3) foods selected and timing patterns of food selection pre VSG and after 12 and 52 weeks in adolescents.

3.2 Methods

Obese adolescent patients older than 12 years, who met eligibility criteria for bariatric surgery (BMI greater than 40 kg /m² or 35 kg /m² with comorbidity), were prospectively included. Patients were assessed for VSG in the Multidisciplinary Obesity Clinic for Children at King Saud University (KSU), Riyadh, Saudi Arabia. Exclusion criteria for the study included lack of understanding of the test

instructions, a diagnosis of diabetes mellitus, pregnancy, breast feeding, substance abuse, psychiatric illness, or allergy to the stimulus ingredients. All non-surgical subjects had BMIs $>25 \text{ kg/m}^2$ and were relatives of the surgical subjects, in order to control for home environments. Anthropometric measurements for all participants were performed before the experiment, weight, height and BMI. Written, informed consent was obtained from all subjects. The study was approved by the Ethics Committee at KSU (Reference E 12-741).

3.2.1 Ad libitum meal study

Ten non-surgical subjects and 13 VSG subjects completed the study between 11:00 and 14:00. The non-surgical subjects were tested twice, 12 weeks apart and the VSG subjects before surgery and after VSG, at 12 and 52 weeks. All subjects had their usual breakfast two hours before each study visit. A customised menu for adolescents from Diet Centre® provided eight choices with comparable nutritional components (mean calories per meal was 1530 kcal and mean weight 1000 g). The menu included traditional food such as biryani rice with beef or kebsa rice with chicken, but also alternatives such as lasagna, spaghetti with tomato and meat, shawarma wraps with beef or chicken, and beef or chicken burger with or without cheese. On the day of recruitment the subjects were also screened for suitability and asked to choose a meal that they would have to consume at all the subsequent visits. At the experimental day the research room was prepared in a standardised way to serve the meal after weighing it using a scale (Appendix 12). The investigator then left the room and the subjects had as much time as they needed to consume their meal, and were informed to call the investigator back into the room once they were done with their meal. During this time a stop watch was used to calculate the duration of meal consumption. At each visit subjects were seated in a quiet private room and consumed their standardised ad libitum test meal with three glasses (750 ml) of water. Meal duration and size were determined. All questionnaires were self-administered with the supervision of the researcher only provided where needed. All anthropometric measures were taken prior to the study each time. Pre-meal hunger and post-meal satiation were measured twice:

a) immediately after the meal and b) one hour later to test whether satiation was maintained using the VAS (Appendix 12).

3.2.2 Attitudes to eating

At each of the above study visits, attitudes towards eating such as cognitive restraint (CR), emotional eating (EE) and uncontrolled eating (UE) were measured using validated three-factor eating questionnaire (TFEQ-21) (244) (Appendix 12).

3.2.3 Food choices and patterns of consumption

Habitual meal patterns over 24 hours were also recorded at each visit using a standardised questionnaire that allowed the analysis of temporal distribution of food intake over 24 hours, meal frequency and the foods selected at different times of the day (Appendix 12). 24h recall methods questionnaire were analysed using the Diet plan 6® software. Food questionnaire were analysed by converting the descriptive data into normative data using the serving size from the American Dietetics Association (ADA) manual. The sample size was calculated to detect an effect size of VSG of 0.85 standard deviations (SD) from the mean VAS rating. With 15 patients in each group this was predicted to permit greater than 90% power to detecting significant differences at the $p < 0.05$ level, using two tailed tests. The effects of sleeve gastrectomy on the study's outcomes have never been examined before. Therefore, the effect size used in the power calculation was informed by similar experiments on patients after RYGB using the same behavioural testing methods at Imperial College London. Comparisons between and within groups were made using the Mann-Witney and Wilcoxon matched pairs test respectively. One-way ANOVA, within the surgical group was performed using repeated measures, Benferoni and the Friedman test respectively. Correlations were made using the Spearman non-parametric test, but the graphs include a parametric linear regression curve for visual comparison. The patient characteristic data were normally distributed and thus t-tests and ANOVA were used for within and between group comparisons for age and BMI, whilst gender comparisons

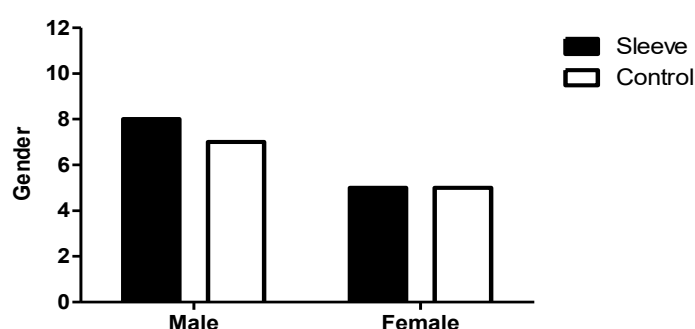
were made with Fisher's exact test. Results are expressed either as mean $\pm$ SEM or median (interquartile range). GraphPad Prism[®] version 5 was used for statistical comparisons, and/or SPSS[®] v22 for the Two Way ANOVA data analysis.

3.3 Results

3.3.1 One Way ANOVA Statistical Analysis

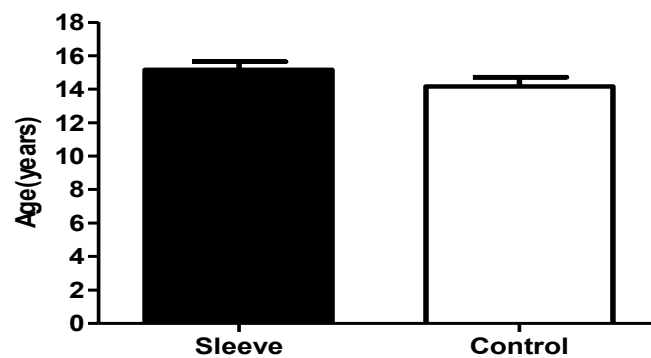
Table 3.3-1 shows the demographics of the participants. All eligible non-surgical participants completed the study (n=10). In the surgical group 17 eligible patients were recruited, and 13 completed the study (Figure 3.3.1-1). Data from completers are reported for both the surgical and non-surgical groups. The mean age within the surgical group was 15.2 ± 0.5 and within the non-surgical group was 14.2 ± 0.5 years ($p=0.2$) (Figure 3.3.1-2); mean BMI was 50.9 ± 2.0 kg/m² and 31 ± 1.8 kg/m², respectively ($p=0.0001$) (Figure 3.3.1-3). There was no bodyweight change in the non-surgical group between the two sessions, but the VSG group reduced their weight from 142 ± 8 kg, to 117 ± 5.5 kg and 95.4 ± 5 kg at 12 and 52 weeks (Figure 3.3.1-4).

Figure 3.3.1-1 Gender distribution in between the groups, VSG vs. Control



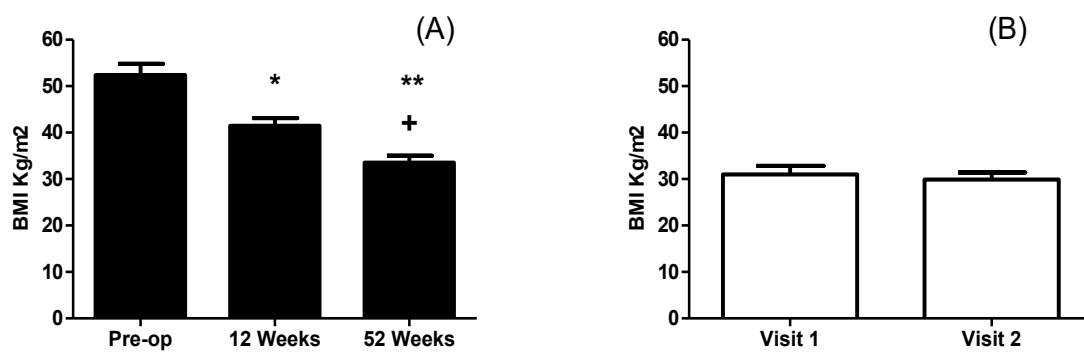
Graph plots the distribution of both male and female in between the groups, VSG vs. Control, they are matching.

Figure 3.3.1-2 Matching Age for both groups VSG vs. Control



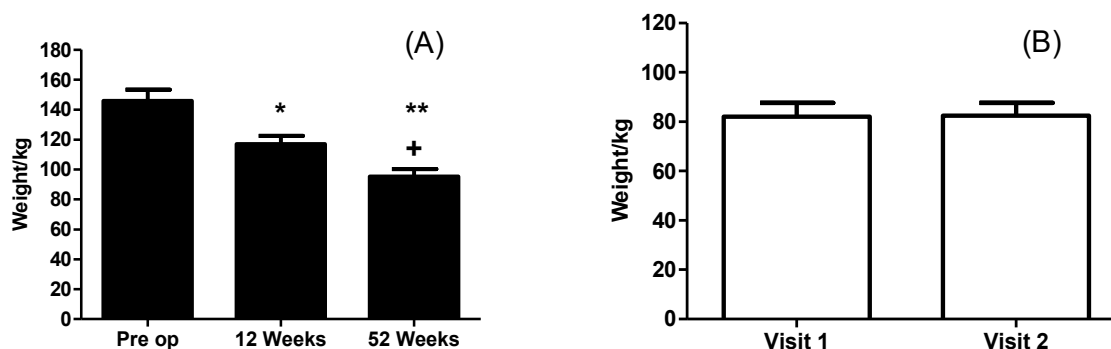
Graph plots the matching age for both groups, VSG vs. Control, they are matching.

Figure 3.3.1-3 Change in BMI pre/post VS



Graph plots the changes in BMI through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit, +52 weeks significantly decreased as compared to 12 weeks. (B) Control groups no changes between the two visits.

Figure 3.3.1-4 Change in Weight pre/post VSG

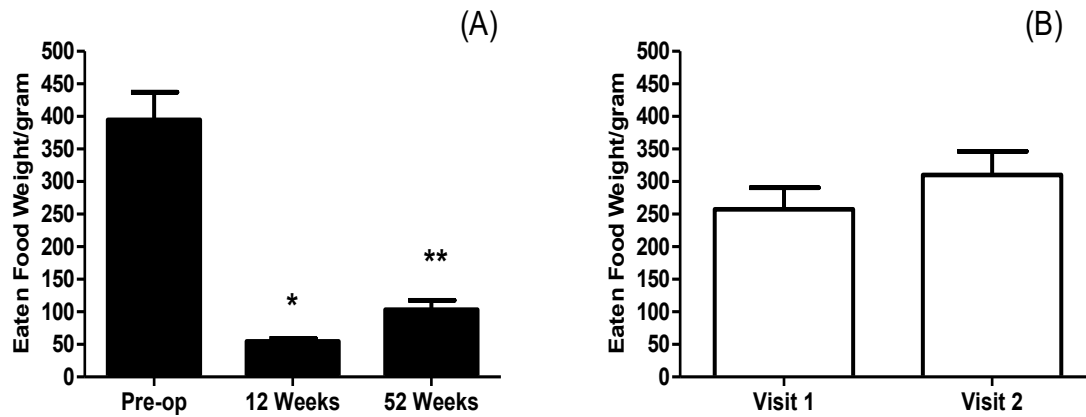


Graph plots the changes in Weight through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit, +52 weeks significantly decreased as compared to 12 weeks. (B) Control groups no changes between the two visits.

3.3.1.1 Ad libitum meal test

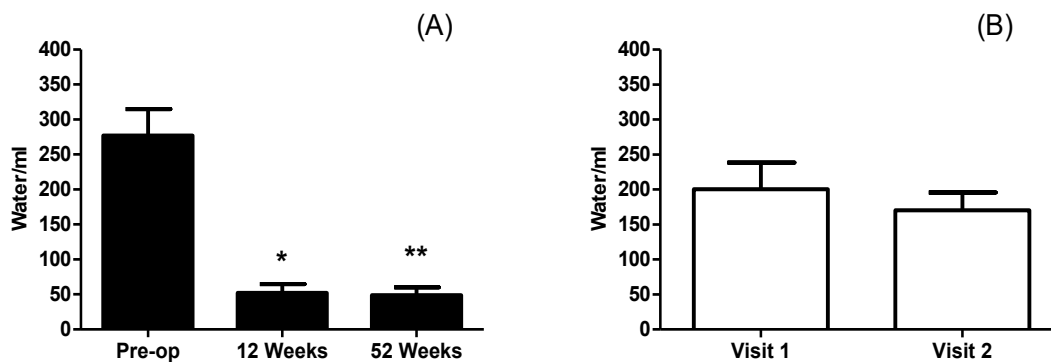
Compared with baseline the weight of food eaten at 12 and 52 weeks reduced after surgery ($p \leq 0.001$), as well as being less than the weight of the food eaten by the non-surgical group ($p \leq 0.02$) (Table 3.3-1, Figure 3.3.1-5). Water intake also decreased from 277 ± 37 ml to 52 ± 13 ml and 49 ± 11 ml after 12 and 52 weeks respectively ($p \leq 0.001$) (Table 3.3-1, Figure 3.3.1-6), while the non-surgical group had no changes in water intake between the two sessions ($p = 0.2$). The rate of eating in the VSG group reduced from 37 ± 5 g/min, to 14 ± 2 g/min and 16 ± 2 g/min at 12 and 52 weeks respectively ($p < 0.001$) (Table 3.3-1, Figure 3.3.1-7). The rate of eating in the non-surgical group changed in the opposite direction by increasing from 26.4 ± 3.6 to 34.5 ± 3.8 g/min ($p \leq 0.02$). Table 3.3-1 show the hunger and craving pre-test reduced at 12 and 52 weeks ($p \leq 0.04$), while craving also decreased at 12 and 52 weeks ($p = 0.03$).

Figure 3.3.1-5 Change in Eaten Food Weight pre/post VSG



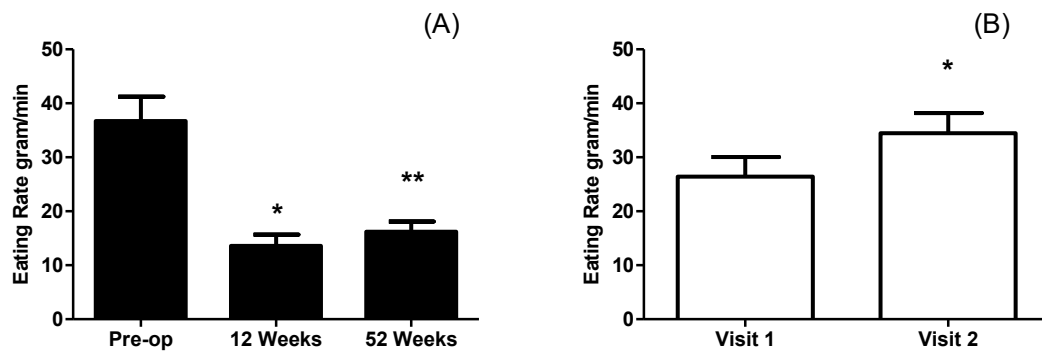
Graph plots the changes in Eaten Food Weight before and after the experiment session through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit. (B) Control groups no changes between the two visits.

Figure 3.3.1-6 Change in Water Intake pre/post VSG



Graph plots the changes in Water Intake before and after the experiment session through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit. (B) Control groups no changes between the two visits.

Figure 3.3.1-7 Change in Eating Rate pre/post VSG

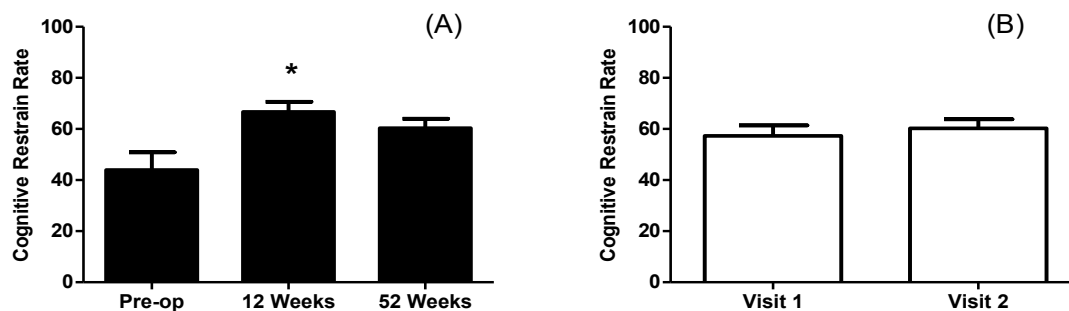


Graph plots the changes in the Eating Rate before and after the experiment session through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit. (B) Control group a significant increase was shown in *2nd visit.

3.3.1.2 Attitude to eating

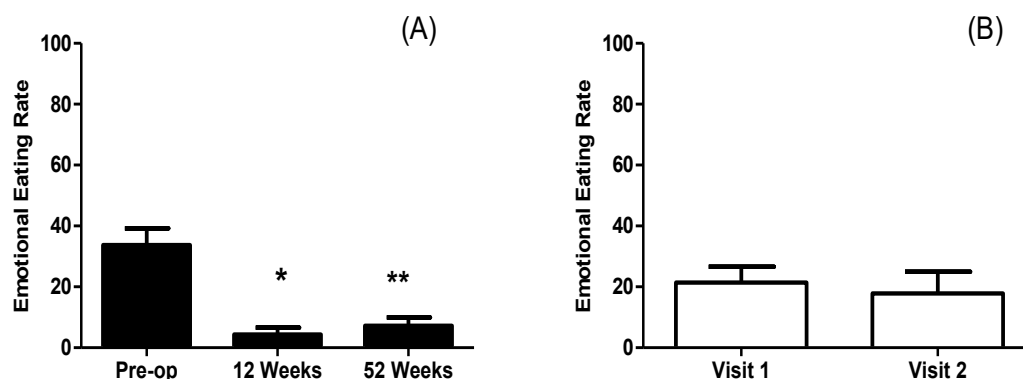
Cognitive restraint (CR), emotional eating (EE) and uncontrolled eating (UE), as assessed by the Three-Factor Eating questionnaire (TEFQ-21), were unchanged in the non-surgical group, but in the VSG group, both EE ($p < 0.001$) and UE ($p < 0.001$) had decreased at 12 and 52 weeks, while CR had increased ($p \leq 0.02$), (Figure 3.3.1-8, Figure 3.3.1-9, Figure 3.3.1-10).

Figure 3.3.1-8 Change in Cognitive Restrain pre/post VSG



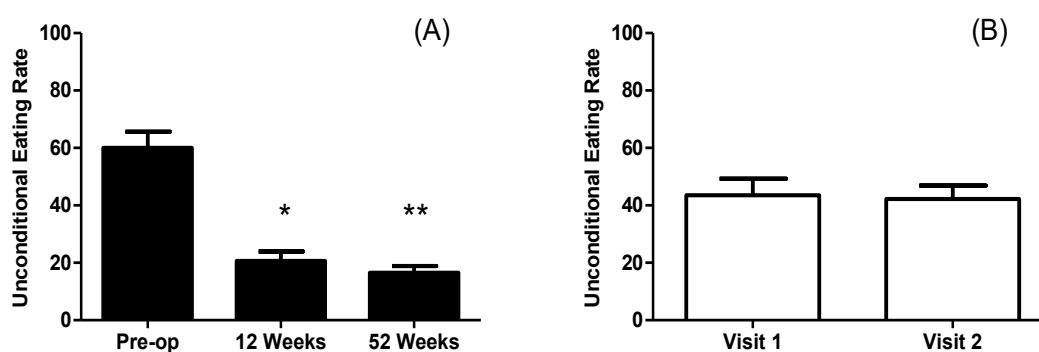
Graph plots the changes in Cognitive Restrain before and after the experiment session through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks is significantly increased as compared to pre-op visit. (B) Control groups no changes between the two visits.

Figure 3.3.1-9 Change in Emotional Eating pre/post VSG



Graph plots the changes in Emotional Eating before and after the experiment session through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit. (B) Control groups no changes between the two visits.

Figure 3.3.1-10 Change in Unconditional Eating pre/post VSG

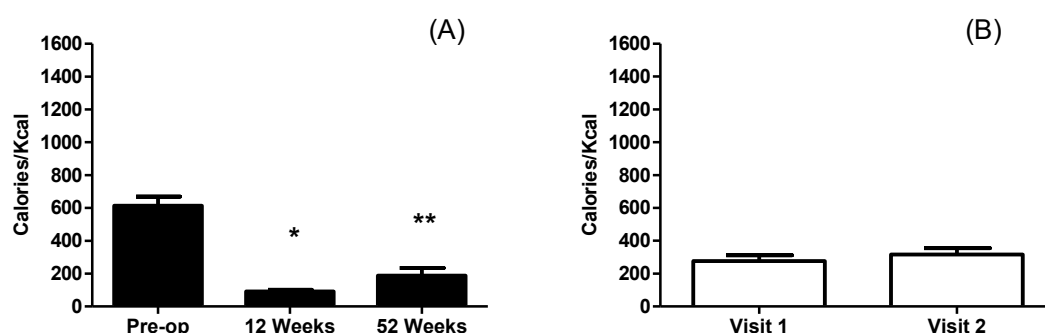


Graph plots the changes in Unconditional Eating before and after the experiment session through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit. (B) Control groups no changes between the two visits.

3.3.1.3 24-hour diet recall

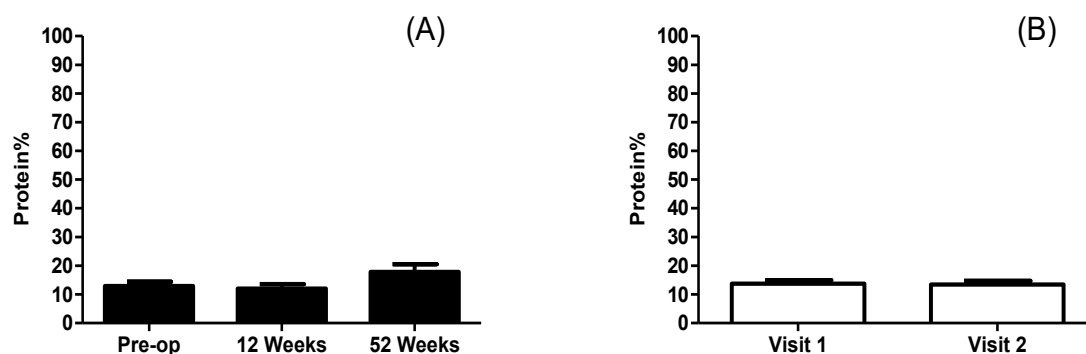
Twenty-four hour calorie intake, according to 24-hour diet recall, decreased after VSG from 3243 $\pm$ 819 kcal to 880 $\pm$ 182 kcal to 1207 $\pm$ 273 kcal at 12 and 52 weeks respectively ($p < 0.001$). No significant change in 24-hour calorie intake was observed in the non-surgical group (2313 $\pm$ 287 vs. 1962 $\pm$ 278 kcal) ($p = 0.3$) (Table 3.3-1, Figure 3.3.1-11). The relative percentages of macronutrients such as protein, fat, and carbohydrates did not change in either the VSG or non-surgical group (Figure 3.3.1-12) (Figure 3.3.1-13) (Figure 3.3.1-14).

Figure 3.3.1-11 Change in Calories consumption pre/post VSG



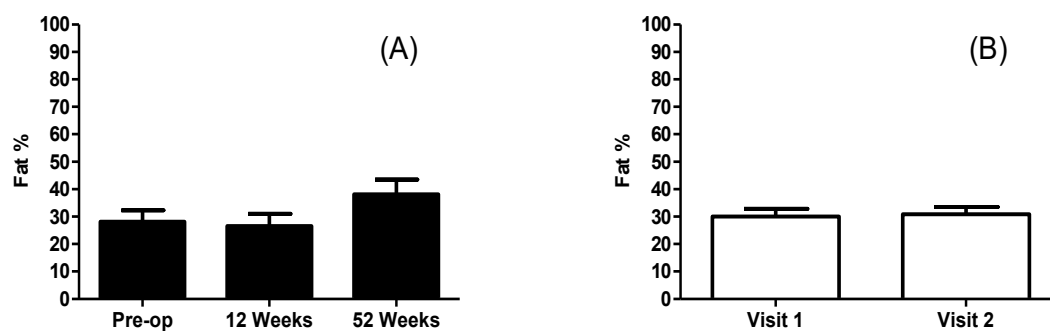
Graph plots the changes in Calories consumption through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visits. (B) Control groups no changes between the two visits.

Figure 3.3.1-12 Change in percentage Protein consumption pre/post VSG



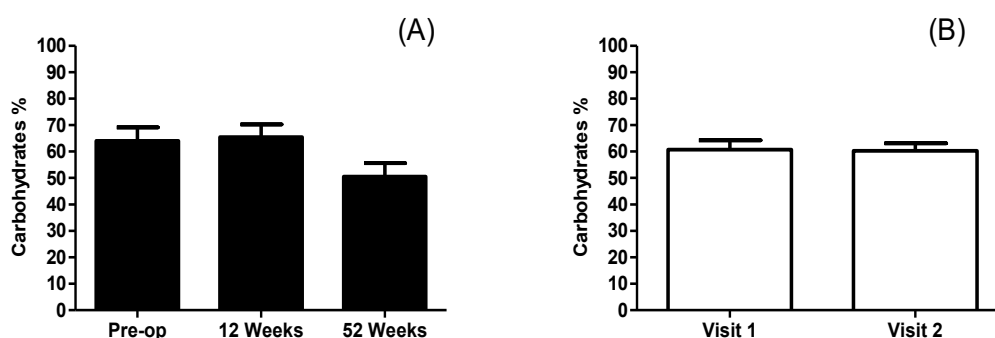
Graph plots changes in percentage Protein consumption. (A) No changes through all three interval visits, baseline, 12 and 52 weeks post VSG. (B) Control groups no changes between the two visits.

Figure 3.3.1-13 Change in percentage Fat consumption pre/post VSG



Graph plots changes in percentage Fat consumption. (A) No changes through all three interval visits, baseline, 12 and 52 weeks post VSG. (B) Control groups no changes between the two visits.

Figure 3.3.1-14 Change in percentage Carbohydrate consumption pre/post VSG



Graph plots changes in percentage Carbohydrate consumption. (A) No changes through all three interval visits, baseline, 12 and 52 weeks post VSG. (B) Control groups no changes between the two visits.

3.3.1.4 Food questionnaires

Food questionnaires, as previously used for patients before and after bariatric surgery by the Swedish Obese Subject Study (563;564), covered most food groups and items, all kind of meats, dairy products, grains, fruits, vegetables, beverages, fast food, and sweets. The non-surgical group had no changes in their choices, preferences and consumption. The VSG group reduced their consumption of foods at 12 and 52 weeks after surgery, compared with pre-surgery, although the 52 weeks intake was greater than 12 weeks intake (Figure 3.3.1-15). Meal size and meal frequency of the main and light meals through the weekdays and weekends decreased at 12 and 52 weeks after VSG (Figure 3.3.1-16). Portion sizes for fats and high glycaemic index carbohydrates decreased at 12 and 52 weeks (Figure 3.3.1-17). The contribution of higher glycaemic index carbohydrates to the overall calorie intake reduced from 44% to 30% and 37% respectively after 12 and 52 weeks after VSG ($p = 0.0001$). While the proportion of lower glycaemic index carbohydrates such as vegetables to the overall calorie intake increased from 22% to 38% and 28% after 12 and 52 weeks respectively ($p = 0.004$). To understand the contribution of foods and their macronutrient content was analysed

preferences broadly in categories defined as fat, higher glycaemic index carbohydrates, lower glycaemic index carbohydrates, proteins and beverages.

Food preferences for fat:

Fast food high in fat, sugar and salt decreased after 12 and 52 weeks, and fried food prepared in the home also decreased at 12 and 52 weeks (Figure 3.3.1-15) (Figure 3.3.1-18). Foods that were previously fried were now grilled, baked, or boiled leading to observed as an increase in each of these at 12 and 52 weeks. The type of fats used in cooking also changed, with less butter, but more vegetable oil at 12 and 52 weeks. Food preferences for higher glycaemic index carbohydrates: White bread was often replaced with whole grain bread as the main source of carbohydrates in their diet (Figure 3.3.1-18).

Food preferences for lower glycaemic index carbohydrates:

Whole grains and vegetables increased at 12 and 52 weeks (Figure 3.3.1-18).

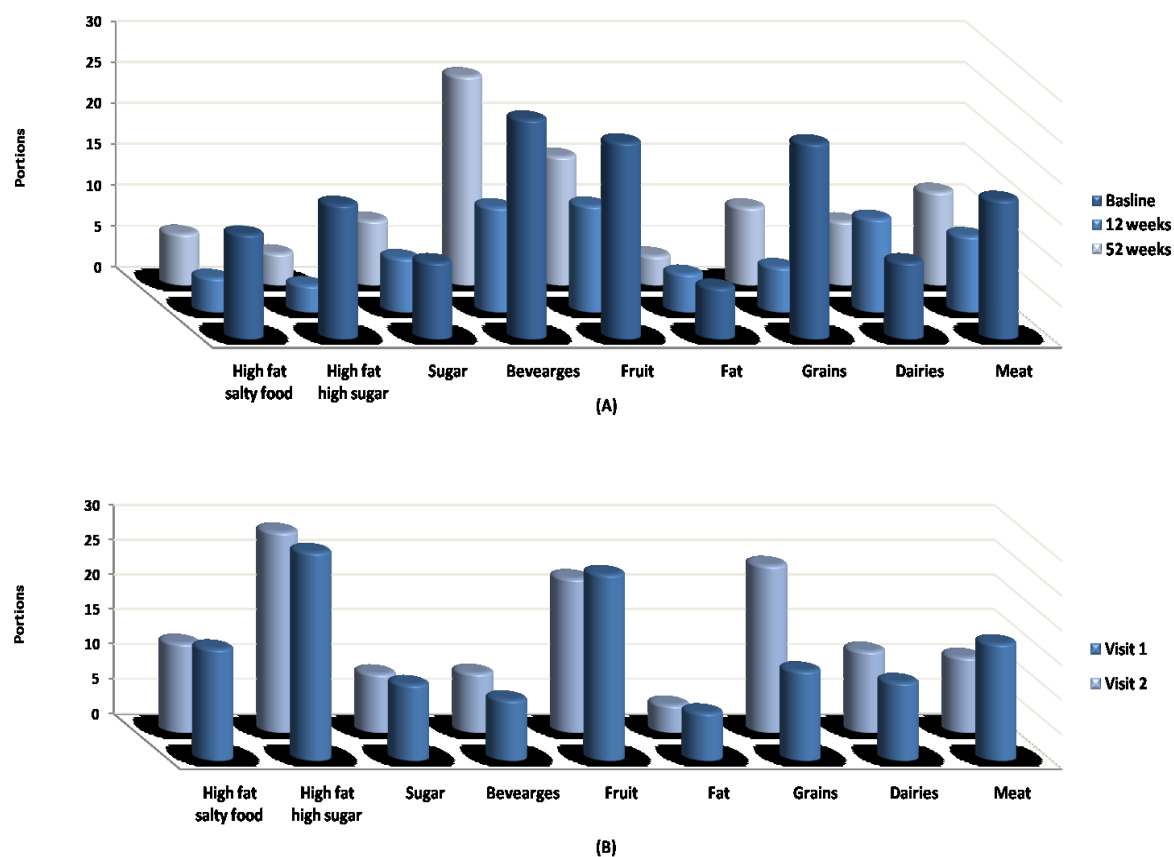
Food preferences for protein:

Cheese, legumes and sea-food increased at 12 weeks and returned to pre surgical levels at 52 weeks. Intake of red meats and chicken decreased at 12 weeks, but returned to pre-surgical levels at 52 weeks (Figure 3.3.1-18).

Beverages:

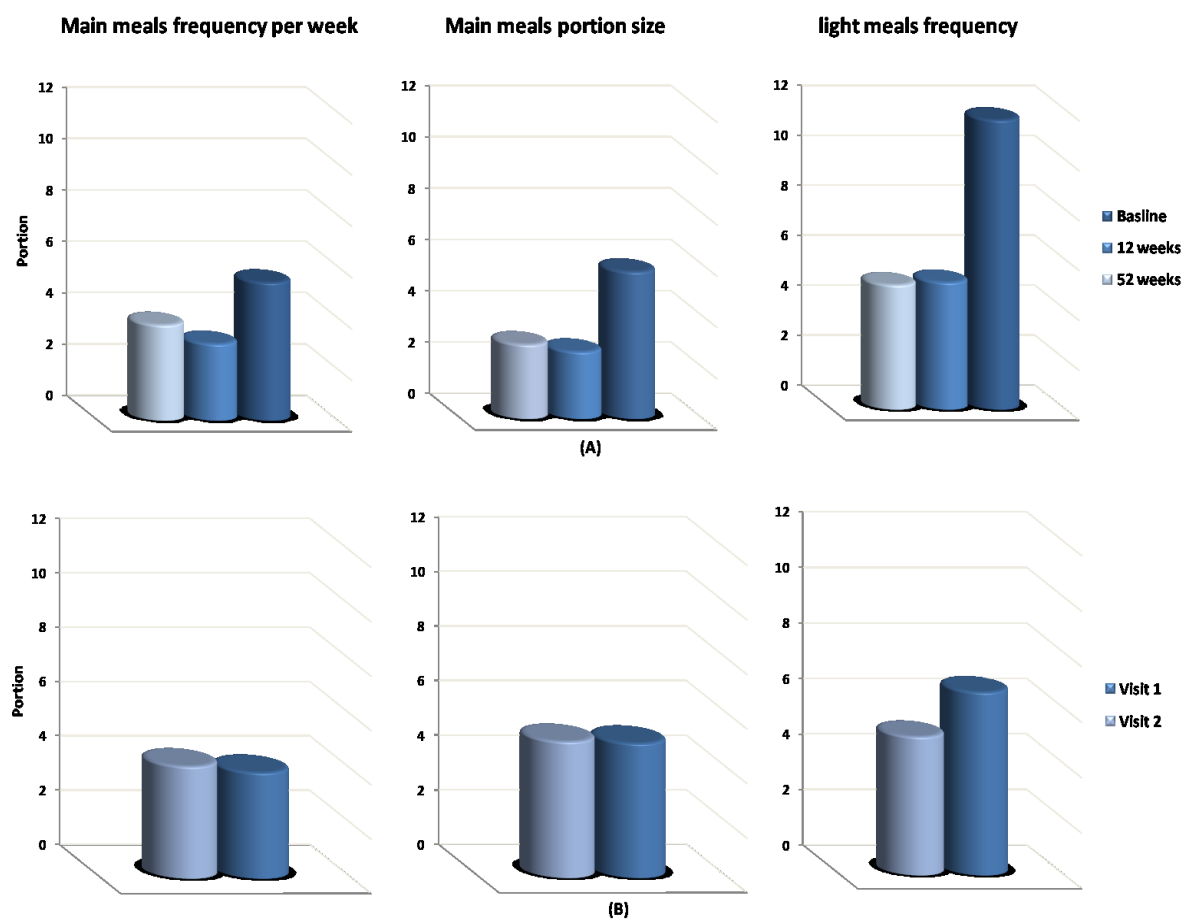
Carbonated beverage consumption decreased at 12 and 52 weeks and non-carbonated beverages increased after 12 and 52 weeks (Figure 3.3.1-19).

Figure 3.3.1-15 Change in percentage Total Consumption pre/post VSG



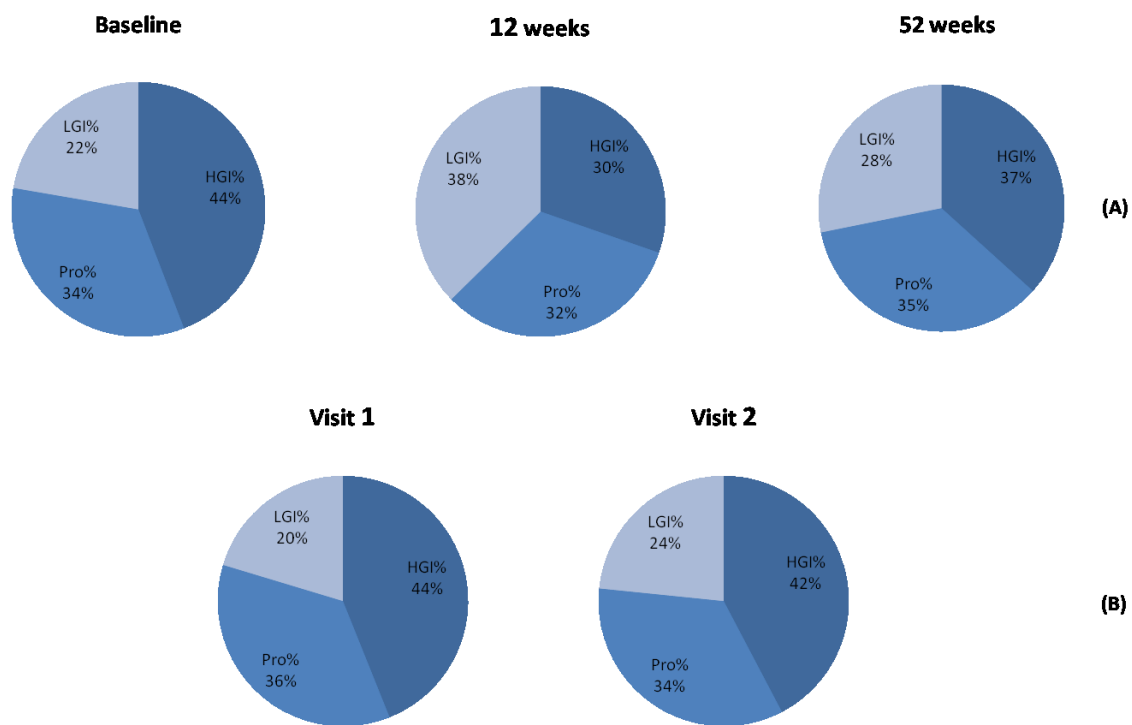
Graph (A) plots the changes in Total consumption through all three interval visits, baseline, 12 and 52 weeks post VSG. (B) Control groups no changes between the two visits.

Figure 3.3.1-16 Change in Main meals portion size and Frequency pre/post VSG



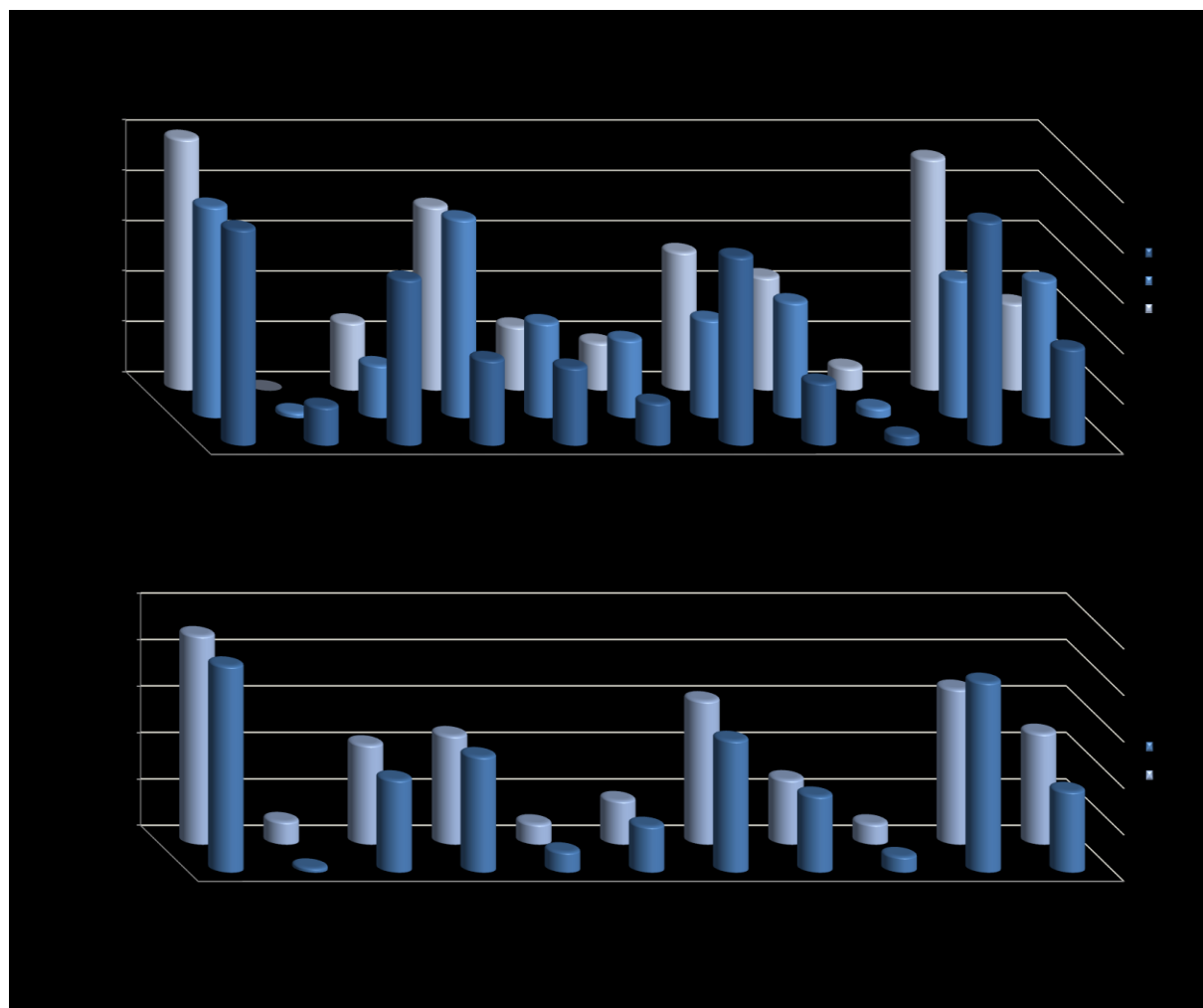
Graph (A) plots the changes in Main meals portion size and frequency and Light meals frequency per week through all three interval visits, baseline, 12 and 52 weeks post VSG. (B) Control groups no changes between the two visits.

Figure 3.3.1-17 Change in portion size for Protein, HGI and LGI pre/post VSG



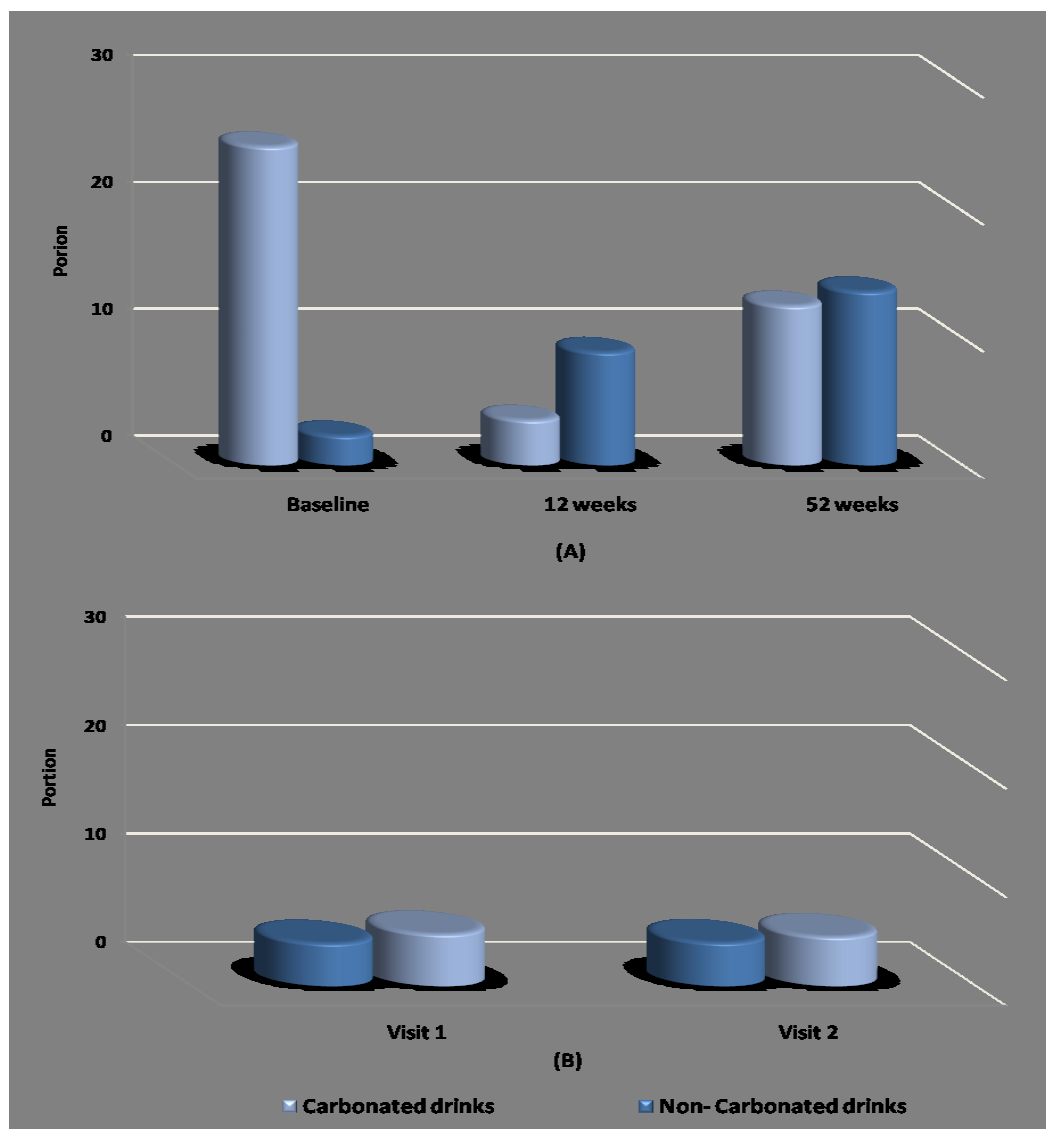
Pie chart (A) plots the changes in the portion size for Protein, HGI and LGI at the main meal for patients at 12 and 52 weeks after VSG. Pie chart (B) plots the changes in the portion size for Protein, HGI and LGI at the main meal for control adolescents' patients at two separate visits.

Figure 3.3.1-18 Changes in different Food Preferences pre/post VSG



Graph (A) plots the changes in Food Preferences through all three interval visits, baseline, 12 and 52 weeks post VSG. (B) Control groups no changes between the two visits.

Figure 3.3.1-19 Changes in consumption of Carbonated beverages vs. Non-carbonated beverages pre/post VSG



Graph (A) plots the changes in consumption of carbonated beverages vs. Non-carbonated beverages through all three interval visits, baseline, 12 and 52 weeks post VSG. (B) Control groups no changes between the two visits.

Table 3.3-1 One Way ANOVA Results

Participant characteristics at baseline and summary of eating behaviour characteristics and visual analogue scale ratings (VAS) at baseline and follow up. All patients were tested at baseline and 12 weeks after enrolment (or surgery), and those undergoing vertical sleeve gastrectomy (VSG) were additionally tested 52 weeks after surgery. Results are expressed as mean $\pm$ SEM or median (interquartile range) depending on normality distribution.

	VSG PRE-OP (N=13)	VSG 12 WEEKS POST-OP (N=13)	VSG 52 WEEKS POST-OP (N=13)	P VALUE WITHIN VSG GROUP	CONTROL VISIT 1 (N=10)	CONTROL VISIT 2 (N=10)	P VALUE WITHIN CONTROL GROUP	P VALUE BETWEEN GROUPS AT BASELINE
Participant Characteristics								
Gender (M/F)	8/5	N/A	N/A	N/A	7/3	N/A	N/A	0.89
Age (years)	15.2 $\pm$ 0.5	N/A	N/A	N/A	14.2 $\pm$ 0.5	N/A	N/A	0.18
BMI (kg/m ²)	52.4 $\pm$ 2.4	41.5 $\pm$ 1.7	33.5 $\pm$ 1.5	*0.0001	31.0 $\pm$ 1.8	29.9 $\pm$ 1.5	0.9	*0.0001
Food Weight Calculations								
Food wt pre-test (g)	974 $\pm$ 102	961 $\pm$ 105	974 $\pm$ 133	0.73	1087 $\pm$ 106	1145 $\pm$ 131	0.27	0.44
Food wt post-test (g)	579 $\pm$ 85	907 $\pm$ 103	871 $\pm$ 134	*0.04	830 $\pm$ 122	835 $\pm$ 118	0.46	0.08
Eaten food wt (g)	395 $\pm$ 42	55 $\pm$ 4.0	103 $\pm$ 15.0	*$\leq$0.0001	257 $\pm$ 34	310 $\pm$ 36	0.25	*0.02
Eating rate (g/m)	36.7 $\pm$ 4.5	13.6 $\pm$ 2.1	16.2 $\pm$ 1.9	*$\leq$0.0001	26.4 $\pm$ 3.6	34.5 $\pm$ 3.8	*0.02	0.13
Water (ml)	277 $\pm$ 37	52 $\pm$ 13	49 $\pm$ 11	*$\leq$0.0001	200 $\pm$ 38	171 $\pm$ 25	0.57	0.16
Duration (m)	12.1 $\pm$ 1.4	5.2 $\pm$ 0.9	6.5 $\pm$ 1.0	*0.008	10.8 $\pm$ 1.1	9.2 $\pm$ 0.7	0.32	0.22
TFEQ-21 Rating Scale								
Cognitive Restrains	43.9 $\pm$ 7.0	66.7 $\pm$ 4.0	60.3 $\pm$ 3.8	*0.02	57.3 $\pm$ 4.0	60.2 $\pm$ 3.6	0.43	0.11
Emotional Eating	33.7 $\pm$ 5.5	4.4 $\pm$ 2.2	7.2 $\pm$ 2.8	*0.0005	21.3 $\pm$ 5.3	17.9 $\pm$ 7.1	0.29	0.12
Unconditional Eating	60 $\pm$ 5.6	20.6 $\pm$ 3.3	16.5 $\pm$ 2.4	*0.0001	43.5 $\pm$ 5.8	42.2 $\pm$ 4.7	0.54	*0.05

	VSG	VSG	VSG	P VALUE	CONTROL	CONTROL	P VALUE	P VALUE
	PRE-OP	12 WEEKS	52 WEEKS	WITHIN VSG	VISIT 1	VISIT 2	WITHIN	BETWEEN
	(N=13)	POST-OP	POST-OP	GROUP	(N=10)	(N=10)	CONTROL	GROUPS AT
		(N=13)	(N=13)				GROUP	BASELINE
Macronutrients Consumption From 24h								
Calories	3243±819	880±182	1207±273	*0.0006	2313±287	1962±278	0.27	0.72
Protein %	12.9±1.5	12.0±1.6	17.9±2.7	0.09	13.8±1.2	13.5±1.2	0.67	0.66
Fat %	28.1±4.2	26.5±4.5	38.1±5.5	0.58	30.1±2.8	30.0±2.7	0.47	0.70
Carbohydrates %	64.0±5.1	65.5±4.9	50.6±5.1	0.07	60.7±3.6	60.3±2.9	0.64	0.60
Visual Analogue Scale Ratings								
Pre-Meal								
Crave pre – test (cm)	62.7±6.4	32.0±6.0	51.5±7.4	*0.04	55.7±6.5	65.4±5.7	0.39	0.49
Hunger pre – test (cm)	55.7±7.2	32.9±8.5	47.1±7.3	*0.006	41.8±6.5	59.1±7.7	0.05	0.16
Satisfaction pre – test (cm)	88.2±5.6	89.5±3.3	75.8±7.1	0.43	81.0±6.3	80.4±8.4	0.91	0.42

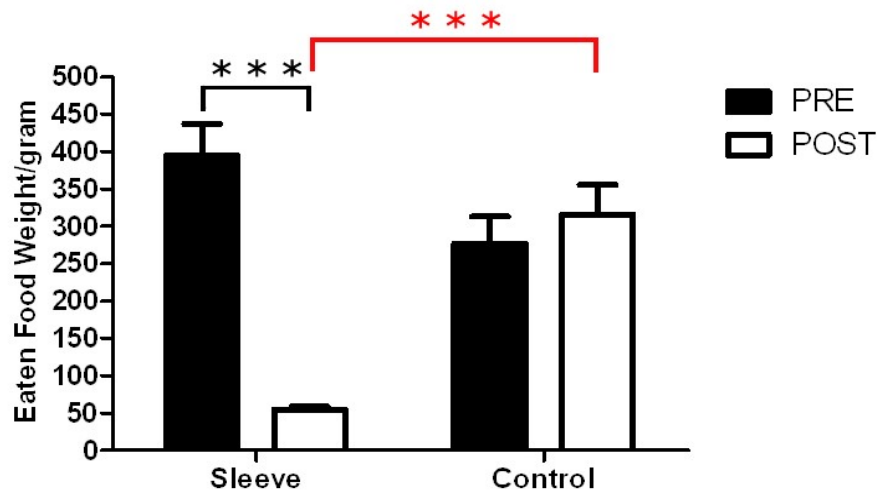
	VSG	VSG	VSG	P VALUE	CONTROL	CONTROL	P VALUE	P VALUE
	PRE-OP	12 WEEKS	52 WEEKS	WITHIN VSG	VISIT 1	VISIT 2	WITHIN	BETWEEN
	(N=13)	POST-OP	POST-OP	GROUP	(N=10)	(N=10)	CONTROL	GROUPS AT
		(N=13)	(N=13)				GROUP	BASELINE
"Food amount" pre – test (cm)	61.6±6.7	29.3±6.0	40.5±6.6	0.09	47.4±5.8	54.4±6.3	0.52	0.12
Visual Analogue Scale Ratings								
Post-Meal								
Crave post – test (cm)	23.6±8.9	4.5±1.8	2.5±1.5	*0.03	6.1±2.9	7.7±4.9	0.81	0.07
Hunger post – test (cm)	8.2±4.9	4.4±1.5	9.7±7.6	0.35	3.9±1.9	5.4±3.3	1.0	0.55
Satisfaction post – test (cm)	93.6±2.9	83.2±6.7	77.2±9.6	0.50	91.5±4.4	95.3±2.7	0.57	0.77
"Food amount" post – test (cm)	10.6±3.8	3.8±1.3	10.2±4.1	0.90	4.8±2.9	10.2±6.4	0.94	0.26
"How Good the food" post – test (cm)	89.3±3.7	88.3±5.2	92.7±3.8	0.42	89.3±4.1	93.6±2.1	0.32	1.0
Visual Analogue Scale Ratings 1hour Post-Meal								
Crave 1hpost – test (cm)	15.1±5.3	16.1±4.6	21.9±6.6	0.53	11.0±3.6	11.3±4.9	0.64	0.53
Hunger 1hpost – test (cm)	12.5±4.9	12.9±4.0	16.4±4.1	0.48	17.8±8.4	2.8±1.3	*0.04	1.0
Satisfaction 1hpost – test (cm)	84.6±5.2	91.6±4.3	87.9±5.5	0.59	93.2±4.1	99.8±0.1	0.06	0.19
"Food amount" 1hpost – test (cm)	15.2±4.7	12.2±3.2	17.2±5.2	0.67	8.8±3.1	9.0±4.0	0.63	0.26

3.3.2 Two Way ANOVA Statistical Analysis

3.3.2.1 Ad libitum meal test

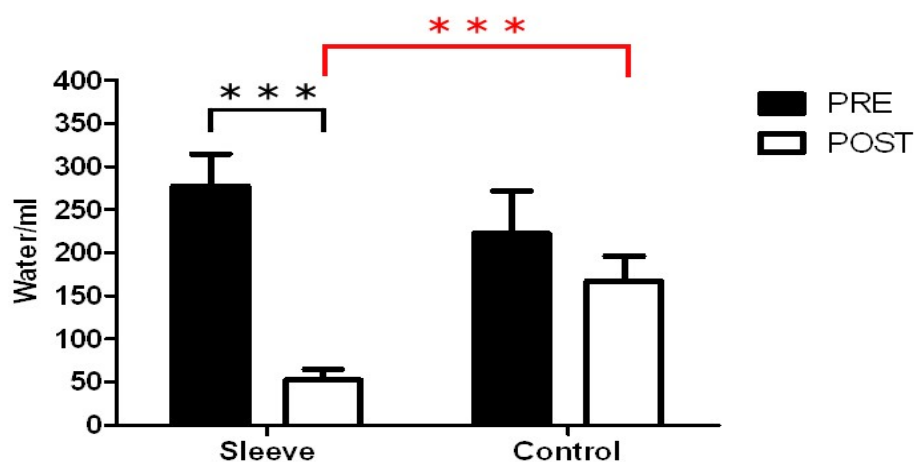
The 2-way repeated measures ANOVA used to study the comparison between groups (VSG vs. Control) and within Group comparisons to examine the Time effect (pre-op vs post-op) on the variables (Table 3.3-2). Post hoc effects of Time within each group was illustrate-according to the Time x Group interaction effect (Table 3.3-3). Meal size and eating rate were reduced significantly after 12 weeks of surgery in the VSG adolescent patients. The overall repeated measures ANOVA for meal size (eaten food): Group $F(1,21)= 5.4$, $p \leq 0.01$, Time $F(1,21)= 4.0$, $p \leq 0.05$, Group x Time $F(1,21)= 24.4$, $p \leq 0.001$. (* $p = 0.001$) with post-hoc Bonferroni significant differences test (Figure 3.3.2-1). The eating rate didn't show any differences between groups $F(1,21)= 2.9$, $p=0.07$ and between visits $F(1,21)= 0.53$, $p=0.47$, but the interaction between Group and Time presented a significant result $F(1,21)= 18.17$, $p \leq 0.001$. (* $p= 0.001$) with post-hoc Bonferroni significant differences test (Figure 3.3.2-3). The water intake didn't show any differences between groups $F(1,21)= 2.4$, $p=0.11$ and between visits $F(1,21)= 2.8$, $p=0.11$, but the interaction between Group and Time presented a significant result $F(1,21)= 4.9$, $p \leq 0.02$. (* $p = 0.001$) with post-hoc Bonferroni significant differences test (Figure 3.3.2-2).

Figure 3.3.2-1 Comparison between groups (VSG vs. Control) and within group to examine time effect on Eaten Food Weight



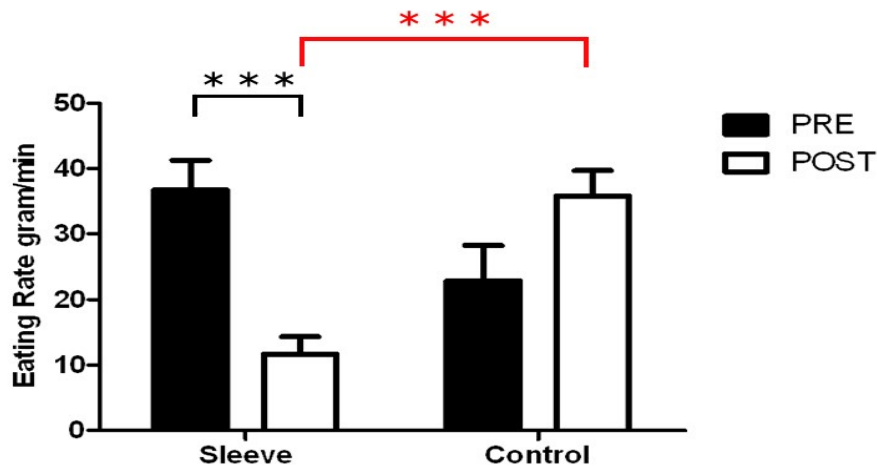
Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs. post-op) on Eaten Food Weight, showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Figure 3.3.2-2 Comparison between groups (VSG vs. Control) and within group to examine time effect on Water Intake



Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs. post-op) on Water Intake, showing the effects of time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Figure 3.3.2-3 Comparison between groups (VSG vs. Control) and within group to examine time effect on Eating Rate

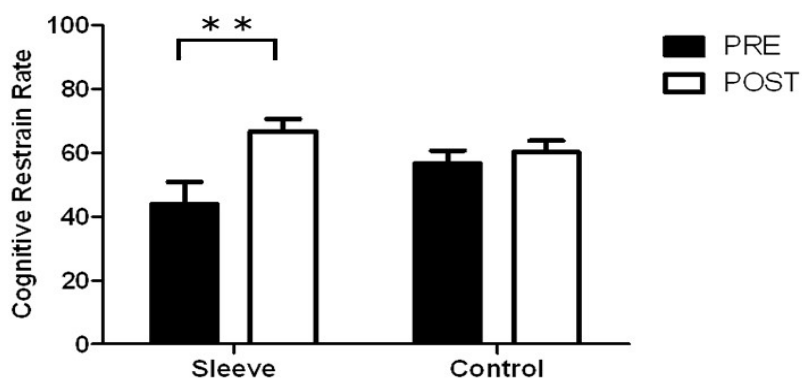


Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs. post-op) on Eating Rate, showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

3.3.2.2 Attitude to eating

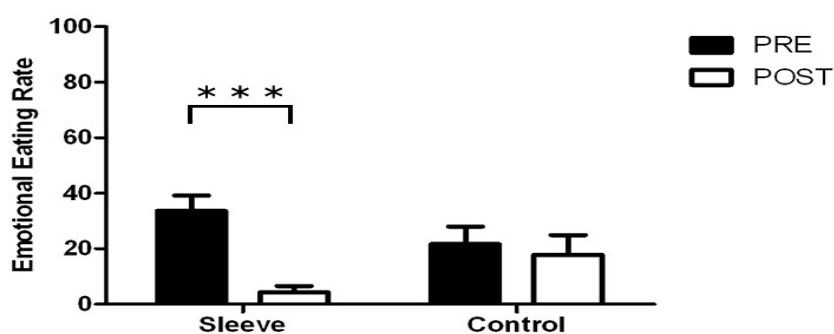
Attitudes towards eating such as cognitive restraint (CR), emotional eating (EE), and uncontrolled eating (UE) did show significant differences after 12 weeks in VSG patients. CR increased and was different between groups $F(1,21)=15$, $p \leq 0.001$ (Figure 3.3.2-4), and the (EE) decreased with an interaction between groups and visits $F(1,21)=6.8$, $p \leq 0.005$ only (Figure 3.3.2-5). Uncontrolled eating (UE) as well was reduced, and the overall repeated measures ANOVA: Group $F(1,21)=4.5$, $p=0.02$, Time $F(1,21)=4.2$, $p \leq 0.05$, Group x Time $F(1,21)=9.7$, $p \leq 0.001$ (Figure 3.3.2-6).

Figure 3.3.2-4 Comparison between groups (VSG vs. Control) and within group to examine time effect on Cognitive Restrain



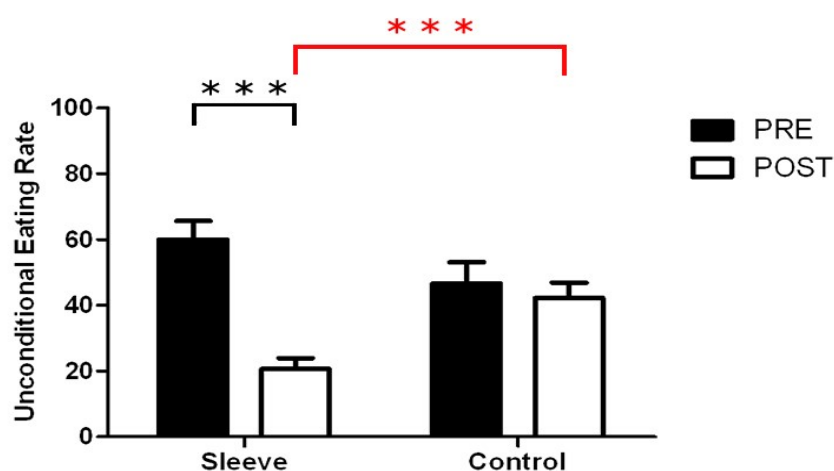
Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs post-op) on Cognitive Restrain (CR), showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Figure 3.3.2-5 Comparison between groups (VSG vs. Control) and within group to examine time effect on Emotional Eating



Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs post-op) on Emotional Eating (EE), showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Figure 3.3.2-6 Comparison between groups (VSG vs. Control) and within group to examine time effect on Unconditional Eating

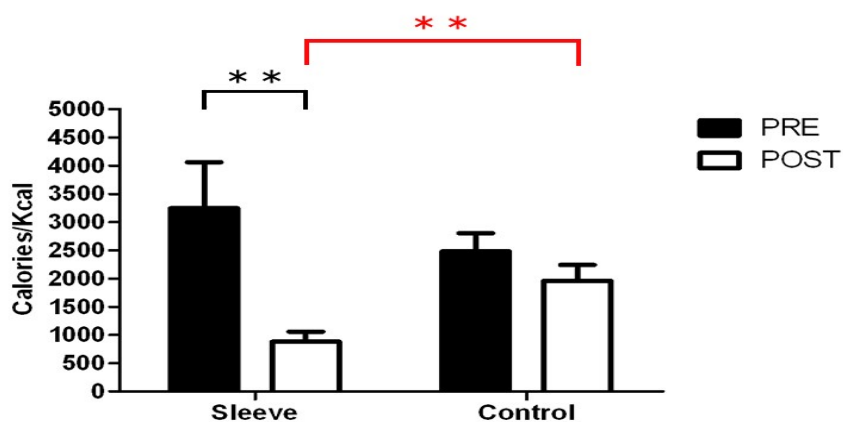


Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs post-op) on Unconditional Eating (UE), showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

3.3.2.3 24 four hour diet recall

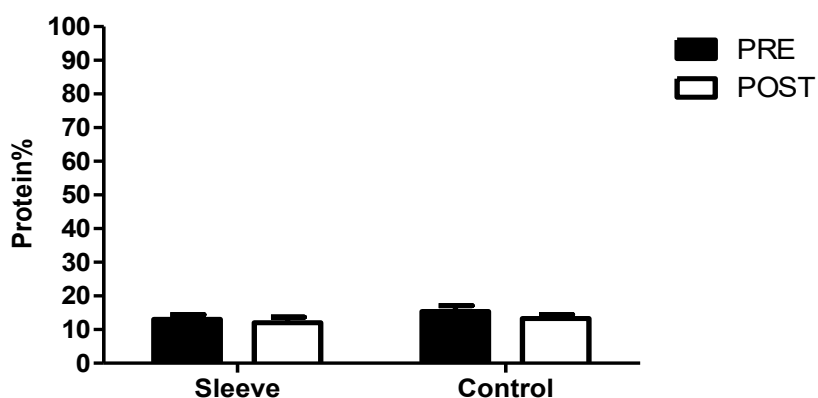
The data showed no differences in the macronutrient component of food as proportion for the carbohydrates, fat, and protein between groups or visits, and no interaction between the groups and time was seen. The overall repeated measures ANOVA for calories intake Group $F(1,21) = 1.4$, $p = 0.27$ Time: $F(1,21) = 1.3$, $p = 0.28$ and Group X Time $F(1,21) = 1.9$, $p = 0.17$) (Figure 3.3.2-7, Figure 3.3.2-8, Figure 3.3.2-9). Given the a priori hypothesis that calories intake will change in the VSG adolescents patients groups after surgery, we illustrate post hoc effects of Time within each group, irrespective of the Time x Group interaction effect. (* $p = 0.002$) with post-hoc Bonferroni significant differences test (Figure 3.3.2-10).

Figure 3.3.2-7 Comparison between groups (VSG vs. Control) and within group to examine time effect on Calories consumed



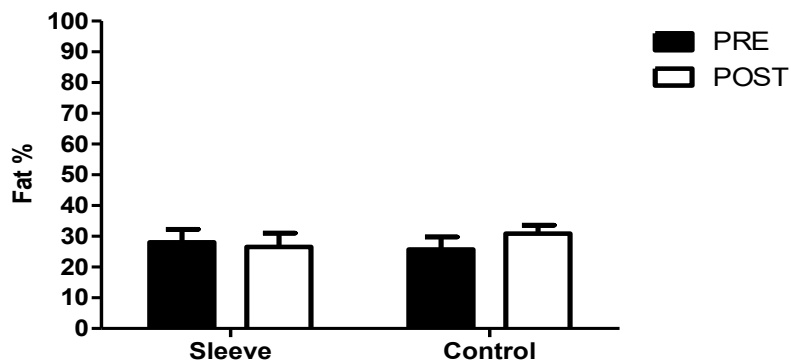
Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs post-op) on Calories consumption, showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Figure 3.3.2-8 Comparison between groups (VSG vs. Control) and within group to examine time effect on Percentage Protein consumed



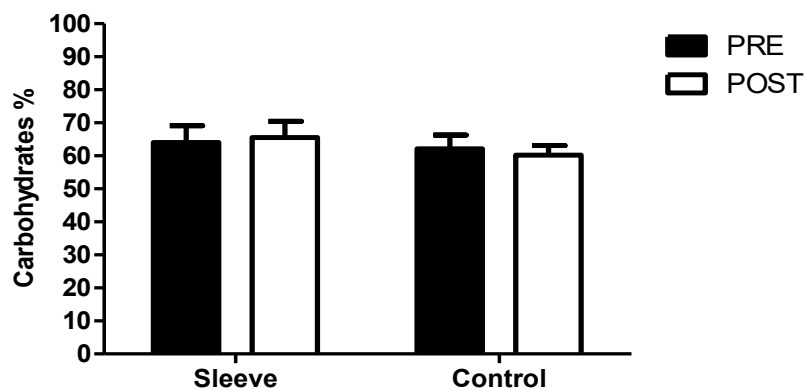
Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs post-op) on percentage protein consumed showing no effects.

Figure 3.3.2-9 Comparison between groups (VSG vs. Control) and within group to examine time effect on Percentage Fat consumed



Comparison between groups (VSG vs. Control) and within Group comparisons to examine the Time effect (pre-op vs post-op) on percentage Fat consumed showing no effects.

Figure 3.3.2-10 Comparison between groups (VSG vs. Control) and within group to examine time effect on Percentage Carbohydrates consumed



Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs. post-op) on percentage Carbohydrates consumed showing no effects.

3.3.2.4 Visual Analogue Scale Ratings

Craving, hunger, satisfaction and wanting all were measured using the VAS. The results showed a reduction in their scale when tested before the test meal was served in the VSG patients as compared to pre-op and control group. The overall repeated measure for craving, hunger, satisfaction and wanting presented a significant interaction between groups and visits, Group X Time $F(1,21)= 4.7, p \leq 0.02$, $F(1,21)= 4.6, p \leq 0.02$, $F(1,21)= 4.7, p \leq 0.02$, and $F(1,21)= 4.7, p \leq 0.02$ respectively, (* $p \leq 0.01$) with post-hoc Bonferroni significant differences test. AS that was filled immediately after they finished their meal didn't show any differences. One hour after consuming their meal, the VSG patients were less satisfied as compared to the controls, Group $F(1,21)=25.9, p \leq 0.001$.(* $p= 0.06$) with post-hoc Bonferroni significant differences test.

Table 3.3-2 Two Way ANOVA Results

Two Way ANOVA results for Participant characteristics at baseline and 12 weeks. A summary of eating behaviour characteristics after Vertical Sleeve Gastrectomy (VSG). Results are expressed as mean +/- SEM or median (interquartile range) depending on normality distribution.

	CONTROLS		SLEEVE		ANOVA					
	PRE	POST	PRE	POST	GROUP		TIME		GROUP X TIME	
Number	10	10	13	13	F ^a	P ^b	F ^a	P ^b	F ^a	P ^b
Participant Characteristics										
Age (years)	14.2±0.5	N/A	15.2±0.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Height (m)	1.64±0.03	1.65±0.03	1.67±0.3	1.68±0.03	0.55	0.46	9.2	0.006	0.08	0.77
BMI (kg/m ²)	30.4±2.3	30.2±1.8	52.4±2	41.5±1.6	37.9	*≤0.001	92.1	*≤0.001	85.3	*≤0.001
Weight (kg)	82.1±7.4	82.5±5.8	145.8±6.5	117±5.1	31.5	*≤0.001	93.6	*≤0.001	98.9	*≤0.001
Food Calculations										
Food wt pre-test (g)	1079.4±118.6	1156.2±130.6	973.7±104	961.2±114.5	4.05	*≤0.033	0.065	0.80	0.42	0.66
Eaten food wt (g)	277±43.5	316±26.1	395±38.1	54.8±22.9	5.4	*≤0.01	4.5	*≤0.05	24.4	*≤0.001
Eating rate (g/m)	22.7±5.3	35.8±3.4	36.7±4.6	11.6±3	2.94	0.075	0.53	0.47	18.17	*≤0.001
Water (ml)	203±43.7	162.5±20.6	277.3±38.3	52.1±18.1	2.4	0.11	2.8	0.11	4.9	*0.02
Duration (m)	10.4±1.5	8.9±0.9	12.1±1.3	5.2±0.8	6.5	*0.006	1.7	0.21	2.6	0.09
TFEQ-21 Rating Scale										
Cognitive Restrains	56.6±6.5	60.2±4.1	43.9±5.7	66.7±3.6	15	*≤0.001	0.76	0.39	1.5	0.25
Emotional Eating	21.7±6.3	17.9±5.0	33.7±5.5	4.4±4.4	0.72	0.49	3.2	0.09	6.8	*0.005
Unconditional Eating	46.6±6.4	42.2±4.2	60±5.7	20.6±3.7	4.5	0.02	4.2	*≤0.05	9.7	*≤0.001
Macronutrients Consumption From 24h										
Calories	2483±736	1962±240	3243±646	880±211	1.4	0.27	1.3	0.28	1.9	0.17
Protein %	0.15±0.016	0.133±0.017	0.128±0.014	0.125±0.014	0.98	0.39	0.3	0.56	0.1	0.88
Fat %	0.292±0.043	0.309±0.046	0.288±0.036	0.275±0.038	0.97	0.39	0.2	0.67	0.2	0.83
Carbohydrates %	0.603±0.054	0.606±0.049	0.636±0.045	0.639±0.041	1.43	0.26	0.04	0.84	0.03	0.97

	CONTROLS		SLEEVE		ANOVA					
	PRE	POST	PRE	POST	GROUP		TIME		GROUP X TIME	
Number	10	10	13	13	F ^a	P ^b	F ^a	P ^b	F ^a	P ^b
Visual Analogue Scale Pre-Meal										
Crave pre – test (cm)	61.7±6.5	62.5±6.3	62.7±5.7	32±5.5	8	*0.003	1.2	0.3	4.7	*0.02
Hunger pre – test (cm)	43.4±7.5	55.5±8.9	55.7±6.6	32.8±7.8	2.3	0.1	0.13	0.7	4.6	*0.02
Satisfaction pre – test (cm)	50.6±7	50.2±6.2	61.6±6.1	29.3±5.5	4.2	*0.03	1.4	0.3	4.7	*0.02
“Wanting” pre – test (cm)	50.6±7	50.2±6.2	61.6±6.1	29.3±5.4	4.2	*0.03	1.4	0.3	4.7	*0.02
Visual Analogue Scale Post-Meal										
Crave post – test (cm)	7.3±8	7.5±3.9	23.6±7	4.5±3.4	0.86	0.4	0.4	0.5	1.6	0.2
Hunger post – test (cm)	4.7±3.9	5±2.7	8.2±3.9	4.4±2.4	0.3	0.8	0.05	0.8	0.2	0.8
Satisfaction post – test (cm)	89.9±4.2	96.8±6	93.6±3.7	83.2±5.2	22.3	*≤0.001	0.03	0.9	2.5	0.1
“Food amount” post – test (cm)	5.8±4	9.2±4.7	10.6±3.5	3.8±4.1	0.3	0.8	0.03	0.9	0.8	0.5
"How Good the food" post – test (cm)	87.5±5.3	94.9±4.6	89.3±3.9	88.3±4.1	27.3	*≤0.001	0.14	0.72	0.8	0.5
Visual Analogue Scale 1hour Post-Meal										
Crave 1hpost – test (cm)	12.4±5.3	11.3±5.1	15.1±4.6	16.1±4.4	0.9	0.4	0.001	0.99	0.03	0.97
Hunger 1hpost – test (cm)	21.4±7.6	2.8±3.6	12.5±6.7	13±3.1	0.4	0.7	0.5	0.5	1.7	0.2
Satisfaction 1hpost – test (cm)	91.8±5.5	99.8±3.7	84.6±4.8	91.6±3.3	25.9	*≤0.001	0.8	0.4	0.12	0.9
“ Food amount” 1hpost – test (cm)	10±4.7	9±3.8	15.2±4.1	12.2±3.3	1.0	0.4	0.05	0.8	0.05	0.9

F^a (1, 21) for all ANOVA results.

P^b values for repeated measures ANOVA with Group as between subject factor and Time as within subject factor.

Data presented as mean ± SEM.

Table 3.3-3 Post hoc effects of Time within groups

Post-hoc Bonferroni significant differences test with Two Way ANOVA results for participant characteristics at baseline and 12 weeks. A summary of eating behaviour characteristics after Vertical Sleeve Gastrectomy (VSG). Results are expressed as mean +/- SEM or median (interquartile range) depending on normality distribution Post hoc effects of Time within each group, according to the Time x Group interaction effect.

	CONTROL VS. SLEEVE AT BASELINE		CONTROL VS. SLEEVE AT 12 weeks		CONTROL BASELINE VS. 12 weeks		SLEEVE BASELINE VS. 12 weeks	
	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value
Participant Characteristics								
Age (years)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Height (m)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weight (kg)	-63.8±9.9	*≤0.001	-34.5±7.7	*≤0.001	0.4±2.2	0.86	28.9±1.9	*≤0.001
BMI (kg/m ²)	-21.95±3.1	*≤0.001	-11.2±2.4	*≤0.001	0.21±0.9	0.81	10.9±0.8	*≤0.001
Food Calculations								
Food wt pre-test (g)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Eaten food wt (g)	-117.9±57.8	*≤0.05	261.2±34.7	*≤0.001	39±41	0.35	340.2±36.4	*≤0.001
Eating rate (g/m)	-14.1±7	0.057	24.2±4.5	*≤0.001	13.15±4.8	*≤0.01	25.1±4.2	*≤0.001
Water (ml)	-74.3±58	0.22	110±27.4	*≤0.001	40.5±46.4	0.39	225.2±40.7	*≤0.001
Duration (m)	-1.7±1.69	0.40	3.7±1.2	*0.007	1.5±1.9	0.43	6.8±1.6	*≤0.001
TFEQ-21 Rating Scale								
Cognitive Restrains	12.7±8.7	0.2	-6.5±5.5	0.25	3.6±8.8	0.68	22.8±7.7	*0.008
Emotional Eating	-12±8.4	0.17	13.5±6.7	0.056	3.8±5.4	0.49	29.3±4.8	*≤0.001
Unconditional Eating	-13.4±8.6	0.163	21.6±5.6	*≤0.001	4.4±6.2	0.48	39.4±5.4	*≤0.001
Macronutrients Consumption From 24h								
Calories	-760±979	0.44	1081±320	*0.003	522±751	0.49	2363±659	*0.002
Protein %	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	CONTROL VS. SLEEVE AT BASELINE		CONTROL VS. SLEEVE AT 12 weeks		CONTROL BASELINE VS. 12 weeks		SLEEVE BASELINE VS. 12 weeks	
	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value
Fat %	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Carbohydrates %	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Visual Analogue Scale Pre-Meal								
Crave pre – test (cm)	-0.99±8.6	0.9	30.5±8.4	*≤0.001	0.8±7.9	0.9	30.7±7	*≤0.001
Hunger pre – test (cm)	12.3±10	0.2	22.7±11.8	0.07	12.1±8.7	0.2	22.8±7.6	*0.007
Satisfaction pre – test (cm)	-0.11±9.3	0.2	20.9±8.3	*0.02	0.4±8.1	0.9	32.2±7.1	*≤0.001
“Food amount” pre – test (cm)	-11±9.3	0.2	20.9±8.3	*0.02	0.4±8.1	0.9	32.2±7.1	*≤0.001
Visual Analogue Scale Post-Meal								
Crave post – test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hunger post – test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Satisfaction post – test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
“Food amount” post – test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
"How Good the food" post – test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Visual Analogue Scale 1hour Post-Meal								
Crave 1hpost – test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hunger 1hpost – test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Satisfaction 1hpost – test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
““Food amount”1hpost – test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

3.4 Discussion

This study has demonstrated that VSG changes eating behaviour and, specifically, *ad libitum* meal size, meal duration and rate of eating reduce. Emotional eating and unconditioned eating decreased postoperatively while cognitive restraint increased. Food preferences, as reported by patients, suggest a reduction in fat and high glycaemic index carbohydrates, with an increase in low glycaemic index carbohydrates and unchanged protein consumption after VSG.

Lessons learnt from RYGB

Laurenus et al. showed that 2 years after RYGB, in addition to a considerable reduction in overall energy intake and large difference in food weight, patients reported decreased dietary energy density, with nutritionally beneficial food choices (367). Laurenus further showed that after RYGB, a reduction in *ad libitum* meal size and rate of eating although meal duration remained the same (244). Interactions between eating rate and satiety hormones have also been demonstrated in humans after RYGB (565). VSG resulted in similar observations documented regarding RYGB (268), showing that reduced energy intake was the most important dietary factor contributing to weight loss. After RYGB subjects tend to increase the intake of fruits and vegetables as well as low fat food (362;363).

3.4.1 Ad libitum meal consumption

Strengths of this study include that direct measures were obtained of the portion size, meal duration and eating rate both preoperatively, and at 12 and 52 weeks after VSG when patients consumed healthy palatable low fat popular ready-made meals. A limitation of this study is that the test meals were served in a test center setting, which may not reflect habitual eating habits of obese adolescent patients, although the methods replicated a previous published protocol (244). Eating rate is

positively correlated with BMI (566-568), and reducing eating rate lowers caloric intake and increased satiety (569-571). Possible mechanisms include changes in appetite-regulatory hormones leading to reduced hunger, which in turn may reduce eating rate and energy intake (292;293). Eating rate may also be reduced to attenuate the risk of dumping syndrome, which may occur when high glycaemic index carbohydrates rapidly reach the proximal small intestinal (406). Reports documenting gastric emptying following VSG are inconsistent (461;462), and it is also unclear how often VSG is associated with symptoms of dumping syndrome, but a recent study suggested that symptoms of dumping syndrome occur in almost half of patients 6 weeks after VSG (572).

3.4.2 Attitudes to eating

Changes in attitudes to eating may also alter meal frequency, meal size, eating rate (547;573), and weight loss maintenance (574-576). Individuals may be influenced by psychosocial factors, such as culture, dietary counseling, food preferences, previous experiences of dieting and emotional state (244). The changes in gastrointestinal physiology after VSG may initiate a cognitive process leading the individual to make changes to their behaviour, or leading them to attempt to avoid negative consequences of eating specific foods (406). This learning process may increase cognitive restraint, although the potential extent of such an impact is controversial (546). Little is known about attitudes to eating after VSG (547;548). Furnes et al. compared eating behaviour in rats that had undergone VSG or RYGB and found that the food intake and meal size were reduced after VSG, but not after RYGB. This suggested that the control of food intake was independent of the food reservoir function of the stomach (545). Seeley et al. demonstrated that reductions in meal size post VSG in rats was not a consequence of volume effects, but rather resulted from the activation of satiation pathways in response to nutrients, and particularly in response to fat content (577).

3.4.3 24 hour recall of food choices

The shift shown after VSG, towards smaller meals and increased meal frequency, is difficult to interpret in the context of inconsistent associations between meal frequency and BMI in both normal weight subjects and those with obesity (578-580). Frequent eating has been associated with poorer weight loss after RYGB (581;582), but no data on VSG is currently available. These inconsistent results may be explained by the difficulty in distinguishing between snacking on high calorie dense foods and having more meals of lower fat and glycaemic index after bariatric surgery(583).

3.4.4 Food questionnaires

Energy intake increases depending on the fat content and energy density of the entire diet (549). After VSG, food preferences became healthier, reducing fat and higher glycaemic index carbohydrate intake, both of which may be associated with conditioned avoidance. This part of the study is limited by the reliance on self-reported data from patient-completed questionnaires, although this method has been validated previously. Information was not collected on physical activity and body composition, which may have strengthened the association between lifestyle changes and weight loss. In conclusion, patients reduced their *ad libitum* meal size, meal duration and eating rate. Habitual meal frequency tended to increase with more meals consumed in the mornings. Emotional and unconditional eating decreased while cognitive restraint increased after VSG. Besides a considerable reduction in overall energy intake, patients also reported decreased dietary energy density. After VSG, adolescents with obesity exhibit eating behaviour that promotes and maintains weight loss.

CHAPTER 4

SUCROSE DETECTION AFTER VERTICAL SLEEVE

GASTRECTOMY IN OBESE ADOLESCENTS

4.1 Introduction

Obesity in young people is one of the most serious public health problems worldwide, but specifically in the Gulf area where more than 27% of children and adolescents are overweight or obese (50;51). Obesity at this age is challenging to treat even if treatment is initiated early (58). Moreover the mechanisms preventing an obese adolescent from losing and maintaining weight loss have been elusive, although bariatric surgery such as vertical sleeve gastrectomy (VSG) is successful at achieving long term weight loss (195). Several studies have demonstrated that VSG can be as effective as RYGB for weight loss over two-years (229;562), though longer term data are awaited. The largest series in the world of VSG in children and adolescents has been performed at King Saud University Hospitals, Riyadh, Saudi Arabia and shows that successful medium term weight loss and resolution of co-morbidities occur within the first 2-5 years after surgery (236). Longer-term data are needed to better understand what happens to these patients as they mature into adulthood (236).

Roux-en-Y gastric bypass (RYGB) in humans and rodents leads to changes in food preference and fundamental alterations in taste sensitivity (264;369-371). After RYGB, patients often report idiosyncratic changes in taste perception that involve “sweet” taste, something that may drive selective reduction in food with a high sugar content (269;279;363;518;524;584). The gustatory system is a prime candidate to explain this observation. It remains unclear, however, whether such changes in intake are conditioned or unconditioned. Furthermore, it is unclear whether changes are attributable to either an alteration in the intensity of sensory signals generated by food, or by their altered evaluation in the so called “reward” circuits of the brain, or a combination of both (263;382;384;385). Anecdotal evidence from clinical observation and evidence in rodents after VSG suggest a shift in food preferences. Seeley et al. showed that VSG in rats reduced intake of dietary fat, and shifted preference toward lower caloric-density foods as compared with sham operated rats.

A progressive-ratio (PR) and conditioned taste aversion paradigms demonstrated a reduction in appetitive behaviour and reduced intake of calorie dense foods after VSG in rats. Food choice was compared between VSG- and RYGB-operated rats, and no differences in food choices were seen between these two anatomically diverse bariatric procedures (529). Taste detection thresholds inform us of the functional status of oral sensory receptors and the sensitivity of downstream gustatory circuits (379;380).

Taste detection thresholds are only one basic aspect of taste function and have been shown to vary as a function of genetics, pharmacological treatment, and neural manipulations (515). Circumventing the influence of post-ingestive factors both in animals and humans is important during assessment of taste function. Postingestive effects can be positive (e.g. fullness) or negative (nausea, visceral pain). Hence, two important methodological features to consider include; a) only small volumes of taste solutions must be used and b) immediate responses to the taste stimulus should be measured. Using direct measures of behaviour to study the effects of RYGB on the sensory domain of sweet taste in obese patients using a method of constant stimuli determined detection thresholds to sucrose showed that sweet taste acuity improves after RYGB (i.e. sweet detection thresholds are reduced) (385). The effect of VSG on the sensory domain of sweet taste has not been studied in humans. The objective of this study was to determine whether humans after VSG have changes in sucrose detection thresholds in the context of previous data that showed humans after RYGB have increased sensitivity to sweet. This study examined oral sensory sucrose taste detection thresholds in adolescent patients undergoing VSG and non-operated overweight/obese controls that were matched for age and gender.

4.2 Methods

This prospective study of obese adolescent patients who fulfilled the criteria for having VSG (BMI greater than 40 kg/m² or 35 kg/m² with comorbidity) recruited patients from the Multidisciplinary Obesity Clinic for Children at King Saud University (KSU), Riyadh, Saudi Arabia. Written, informed consent was obtained from all the subjects. The study was approved by the Ethics Committee at KSU (Reference E 12-767). Assessment of sucrose detection thresholds in fourteen obese adolescent subjects was performed two weeks before and 12, and 52 weeks after VSG. Ten non-surgical subjects were tested on two occasions 10-12 weeks apart to ensure no learning occurred in between the test that may alter the outcome. Dietetic advice given to the patients was similar to what was received within the non-surgical weight management program and included advice on healthy eating, avoiding calorie dense foods and increasing physical activity. The patients were reviewed every 3 months for nine months by a clinical dietitian within the multi-disciplinary clinic. The tests were all performed in the morning after an overnight fast of at least 10 hours. Room temperature was kept constant at 21 °C for all test sessions. All solutions were prepared daily using the same distilled still natural mineral water (Bambini distilled still natural baby water, Delta Marketing Co. Ltd., Jeddah, KSA) and presented at room temperature. As per previously validated protocols (381), seven sucrose (Sigma Aldrich, Dorset, UK) concentrations were used in this study: 2.1, 6.25, 12.5, 25, 50, 100 and 300 mM. Concentrations were tested in eight blocks, each block consisting of seven sucrose and seven water stimuli. Sucrose and water stimuli were presented in random order without replacement (Appendix 13). Thus, each of the seven sucrose concentrations was presented once within a block. Fifteen millilitres of water or sucrose stimuli were offered in polystyrene cups and subjects were given a period of five seconds to sample the stimulus in the mouth. Subjects then expectorated the sample and were given additional five seconds to indicate whether the stimulus was water or not by answering the investigators question for each trial "Is this water or not?".

Each stimulus was followed by a thorough ten second water rinse with 30 ml of water, which was expelled before the next stimulus was offered. To maintain attention to the task, the patients were rewarded for correct responses with the presentation of a token and penalized by loss of a token for incorrect responses. The sucrose detection study used the method of constant stimuli in which taste stimuli are presented randomly and performance is assessed allowing for the derivation of a psychometric function. A “hit” was defined as when the subject correctly reported that the stimulus was different from water when sucrose was presented. A “false alarm” (FA) was defined when the subject incorrectly reported that the stimulus was different from water when water was presented. The hit rate for a given sucrose concentration was adjusted for the false alarm rate to derive a “corrected hit rate” using the following equation: $Corrected\ Hit\ Rate = \frac{P(hit) - P(FA)}{1 - P(FA)}$ where $P(hit)$ = the proportion of sucrose trials of a given concentration that were hits, and $P(FA)$ = the proportion of water trials that were false alarms. Thus, when the uncorrected hit rate is equal to the false alarm rate, the corrected hit rate=0. The corrected hit rate values were subjected to two-way analyses of variance (ANOVAs). Because there was very little or no variance around the sample means for the highest three concentrations for the groups both preoperatively and postoperatively, only the scores for the lower 4 concentrations, representing the dynamic range of performance, were used in the ANOVAs. In addition, concentration-response curves were fit to the corrected hit rate values for each subject preoperatively and postoperatively to derive a family of individual psychometric functions using the following logistic equation: $f(x) = a / [1 + 10^{((\log_{10}(x) - c) \times b)}]$ where $\log_{10}(x)$ = $\log_{10}$ concentration, a = the upper asymptote of performance, b = slope, and c = the $\log_{10}$ concentration at 1/2a performance (i.e. EC50). The c parameter was defined as the threshold because it represents the inflection point of the psychometric function and thus optimally represents lateral shifts in sensitivity.

Only c-values of the individual curve fits for the subjects who had fits that accounted for at least 85% of the variance was compared. The shifts in the c parameters were analyzed in a one-way ANOVA. All subjects had curve fits that accounted for at least 85% of the variance and all were included in the analyses of corrected hit rate described above. All other variables were compared with paired/unpaired t-tests or their non-parametric equivalents depending on the normality distribution of the data, with $p \leq 0.05$ used to define statistical significance.

The sample size was calculated to detect an effect size of VSG of 0.85 standard deviations (SD) from the mean VAS rating. With 15 patients in each group this was predicted to permit greater than 90% power to detecting significant differences at the $p < 0.05$ level, using two tailed tests. The effects of sleeve gastrectomy on the study's outcomes have never been examined before. Therefore, the effect size used in the power calculation was informed by similar experiments on patients after RYGB using the same behavioural testing methods at Imperial College London.

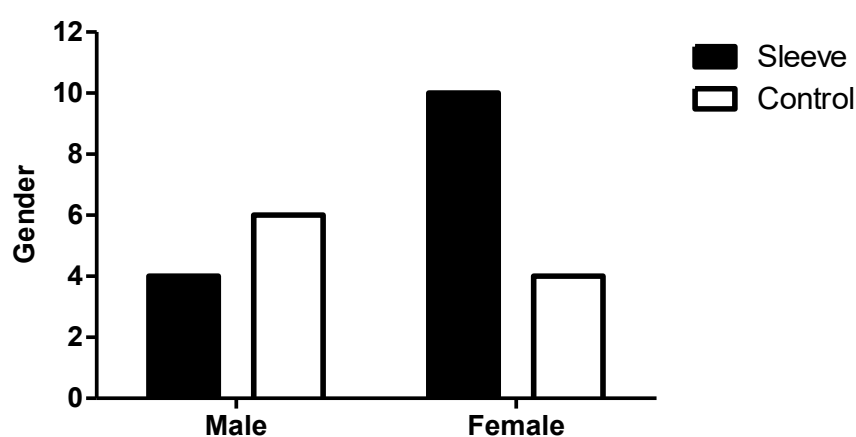
Comparisons between and within groups were made using the Mann-Witney and Wilcoxon matched pairs test respectively. One-way ANOVA, within the surgical group was performed using repeated measures, Benferoni and the Friedman test respectively. Correlations were made using the Spearman non-parametric test, but the graphs include a parametric linear regression curve for visual comparison. The patient characteristic data were normally distributed and thus t-tests and ANOVA were used for within and between group comparisons for age and BMI, whilst gender comparisons were made with Fisher's exact test. Results are expressed either as mean $\pm$ SEM or median (interquartile range). GraphPad Prism[®] version 5 was used for statistical comparisons and/or SPSS[®] v22 for the Two Way ANOVA data analysis and Mypstat[®] (Systat[®] 13).

4.3 Results

4.3.1 One Way ANOVA Statistical Analysis

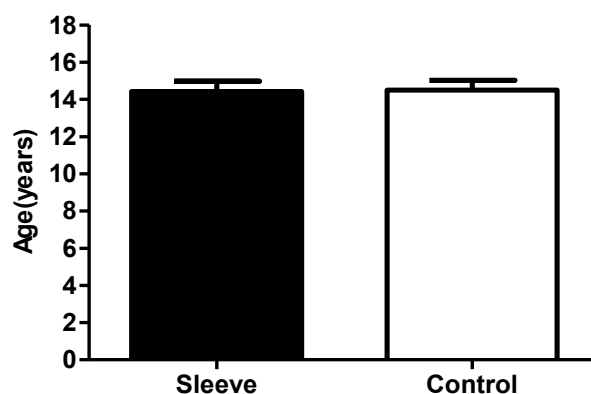
The 14 adolescent patients (Figure 4.3.1-1, Figure 4.3.1-2) after VSG experienced a reduction in their mean body weight from 136.7 ± 5.4 kg to 109.6 ± 5.1 kg and 86.5 ± 4.0 kg after 12 and 52 weeks respectively ($p < 0.001$) (Figure 4.3.1-3) resulting in a BMI reduction from 49.6 ± 1.6 to 39.4 ± 1.5 and 31.0 ± 0.9 kg/m² ($p < 0.001$) (Figure 4.3.1-4). There were no nutritional or surgical complications in the surgical group. In contrast, the 10 non-surgical subjects had a BMI of 32.0 ± 1.6 kg/m² and kept their body weight stable at 89.9 ± 5.4 kg vs. 90.1 ± 5.6 kg, ($p = 0.30$) as shown in (Table 4.3-1).

Figure 4.3.1-1 Gender distribution in between the groups, VSG vs. Control



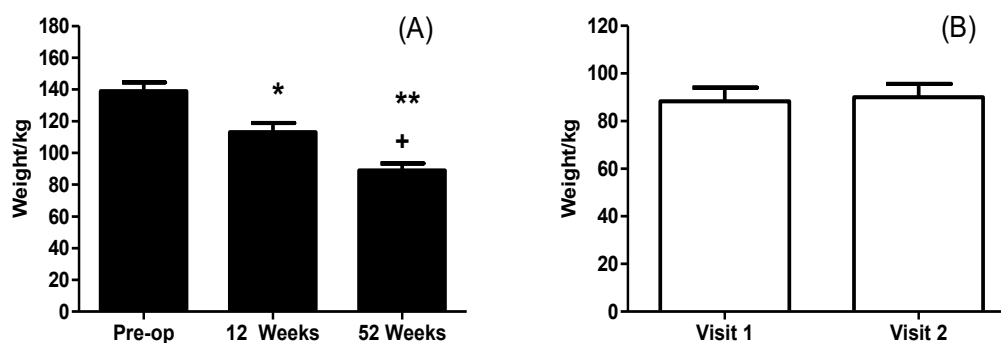
Graph plots the distribution of both male and female in between the groups, VSG vs. Control.

Figure 4.3.1-2 Matching Age for both groups, VSG vs. Control



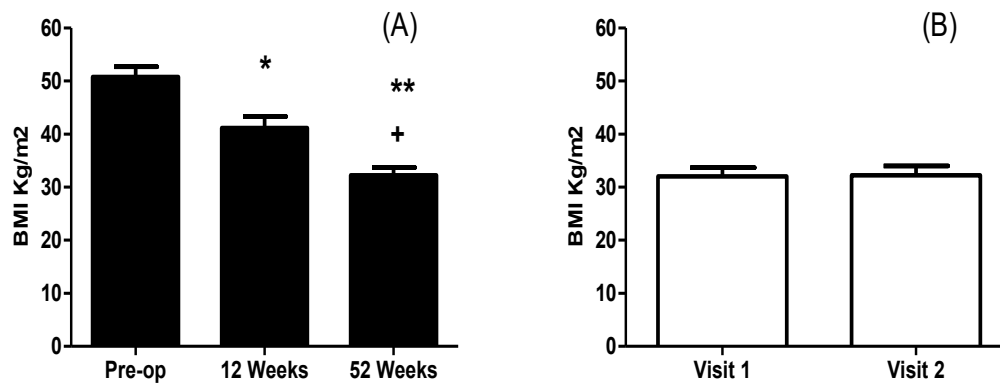
Graph plots the matching age for both groups, VSG vs. Control, they are matching.

Figure 4.3.1-3 Changes in Weight pre/post VSG



Graph plots the changes in Weight through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit, +52 weeks significantly decreased as compared to 12 weeks. (B) Control groups no changes between the two visits.

Figure 4.3.1-4 Changes in BMI pre/post VSG

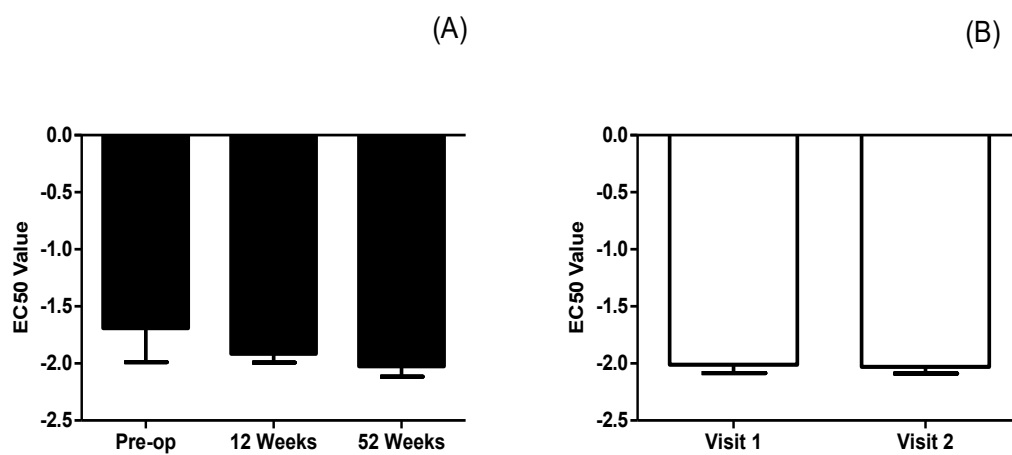


Graph plots the changes in BMI through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit, +52 weeks significantly decreased as compared to 12 weeks. (B) Control groups no changes between the two visits.

4.3.1.1 Corrected hit rate analysis for sucrose taste detection.

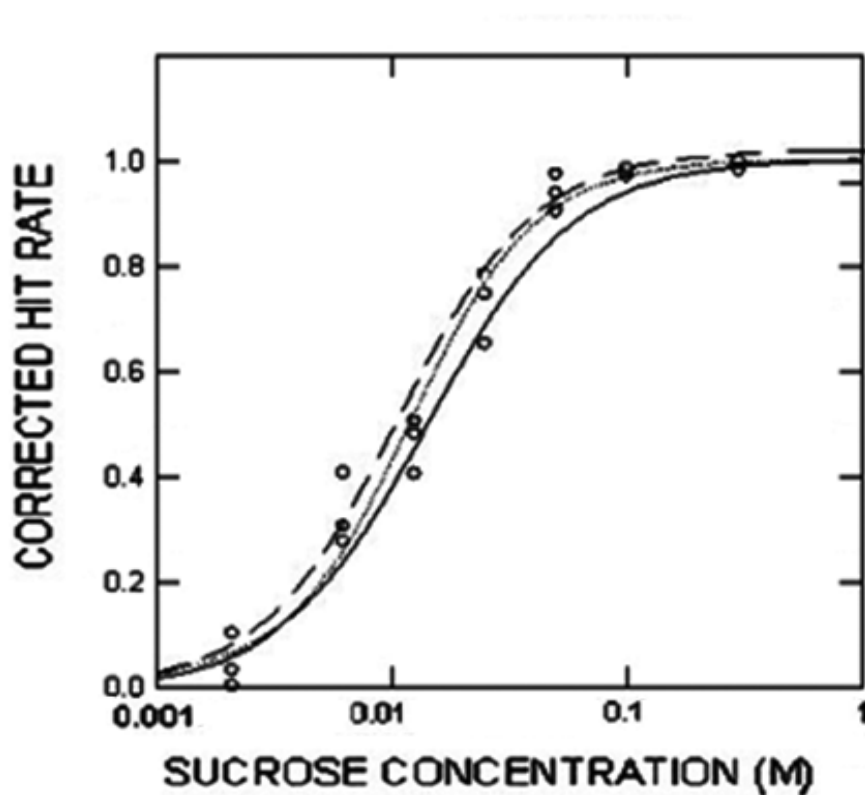
The mean corrected hit rates (proportion of sucrose trials adjusted for false alarm rate; see above for non-surgical subjects and patients pre- and postoperatively (Figure 4.3.1-5, Figure 4.3.1-6) are displayed in (Table 4.3-1). The one-way ANOVA values for comparison of the corrected hit rates pre and postoperatively between visits pre, 12 and 52 weeks post- VSG are also shown in (Figure 4.3.1-6) along with the two visits for the non-surgical group which occurred 12 weeks apart (Figure 4.3.1-6). Preoperatively, there were no differences between controls and patients with no significant main effect of groups, neither an interaction between group and concentration, for the corrected hit rates ($p=0.8$). There was also no difference uncorrected hit rate in the non-surgical group in-between their two visits ($p=0.3$), nor for the VSG group between the three visits ($p=0.2$). The c-value, representing the EC50 (the concentration where subjects achieved the mean corrected hit rate also did not change significantly after VSG either at 12 or 52 weeks (Figure 4.3.1-5).

Figure 4.3.1-5 Changes in Ec50s pre/post VSG



Graph plots changes in EC50s. (A) No changes through all three interval visits, baseline, 12 and 52 weeks post VSG. (B) Control groups no changes between the two visits.

¹Figure 4.3.1-6 Corrected hit rate for sleeve patients pre/op VSG as a function of sucrose concentration.



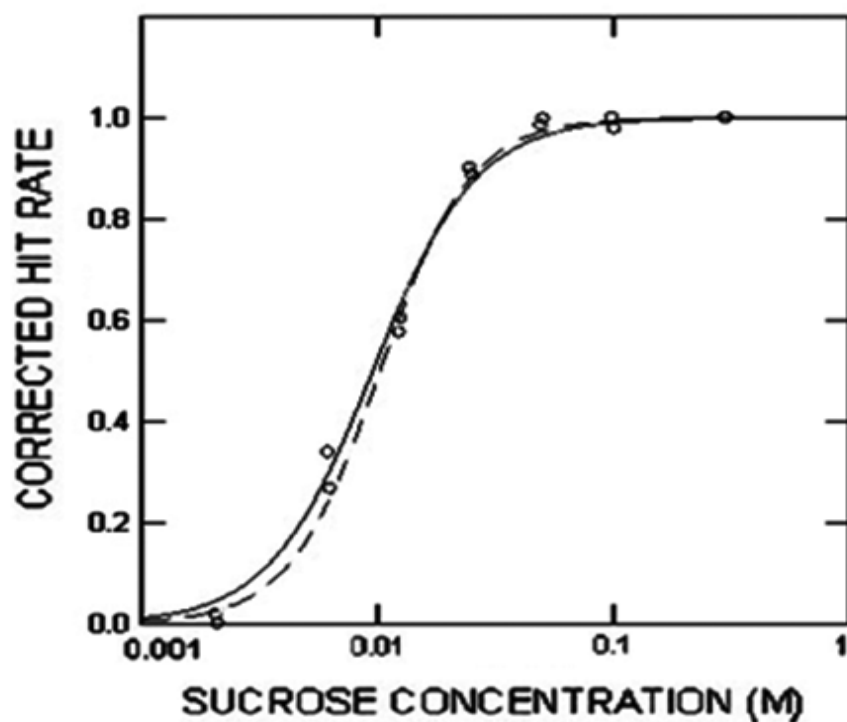
Mean $\pm$ SEM corrected hit rate for VSG patients preoperatively and postoperatively as a function of sucrose concentration. Curves were fit to the mean data points using Eq. (2) in text. The EC50 was derived from the c-parameter in the curve fit and represents the concentration at which the corrected hit rate reaches 50% of the maximum asymptote. No significant changes were shown between the study groups.

¹ Pre-op _____

Post-op 12 weeks

Post-op 52 weeks _ _ _ _ _

²Figure 4.3.1-7 Corrected hit rate for controls in 2 visits as a function of sucrose concentration.



Mean $\pm$ SEM corrected hit rate for controls at visit 1 and 2, as a function of sucrose concentration. Curves were fit to the mean data points using Eq. (2) in text. The EC50 was derived from the c-parameter in the curve fit and represents the concentration at which the corrected hit rate reaches 50% of the maximum asymptote. No significant changes were shown between the study groups.

² Visit 1 _____

Visit 2 _ _ _ _ _

Table 4.3-1 One Way ANOVA Results

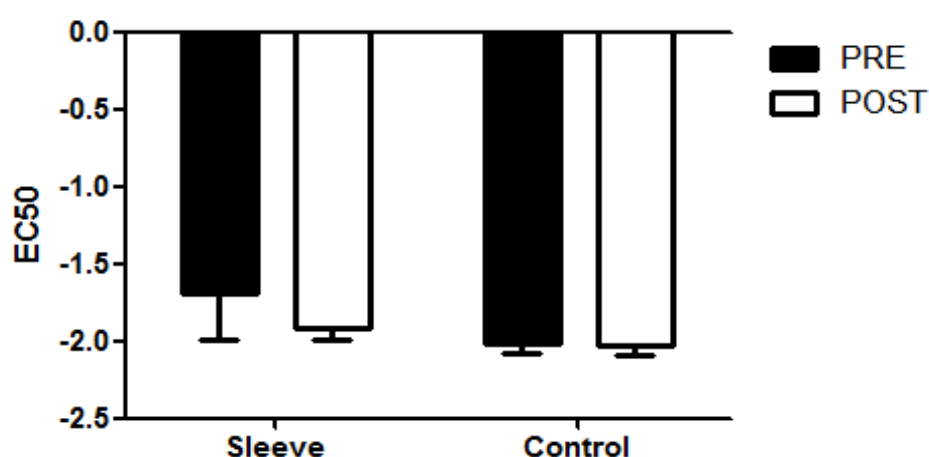
Participant characteristics at baseline and sucrose taste detection thresholds at baseline and follow up. Patients were tested 12 nd 52 weeks after vertical sleeve gastrectomy (VSG), whilst un-operated obese control participants were tested 10-12 weeks apart. Results are expressed as mean $\pm$ SEM or median (interquartile range) depending on normality distribution. Data from all subjects are represented as they all met the criterion of 85% of variance accounted for in the curve fits.

	VSG PRE-OP (N=14)	VSG 12 WEEKS POST-OP (N=14)	VSG 52 WEEKS POST-OP (N=14)	P VALUE WITHIN VSG GROUP	CONTROL VISIT 1 (N=10)	CONTROL VISIT 2 (N=10)	P VALUE WITHIN CONTROL GROUP	P VALUE BETWEEN GROUPS AT BASELINE
Participant Characteristics								
Gender (M/F)	4/10	N/A	N/A	N/A	6/4	N/A	N/A	0.24
Age (years)	15.2 $\pm$ 0.5	N/A	N/A	N/A	15.1 $\pm$ 0.6	N/A	N/A	0.92
BMI (kg/m ²)	49.6 $\pm$ 1.6	39.6 $\pm$ 1.5	31.0 $\pm$ 0.9	*$\leq$0.0001	33.1 $\pm$ 1.8	32.2 $\pm$ 1.8	0.69	*$\leq$0.0001
Tested sucrose taste detection thresholds								
EC50s	-1.7 $\pm$ 0.3	-1.9 $\pm$ 0.1	-2.0 $\pm$ 0.1	0.60	15.2 $\pm$ 0.5	15.1 $\pm$ 0.6	0.69	0.38

4.3.2 Two Way ANOVA Statistical Analysis

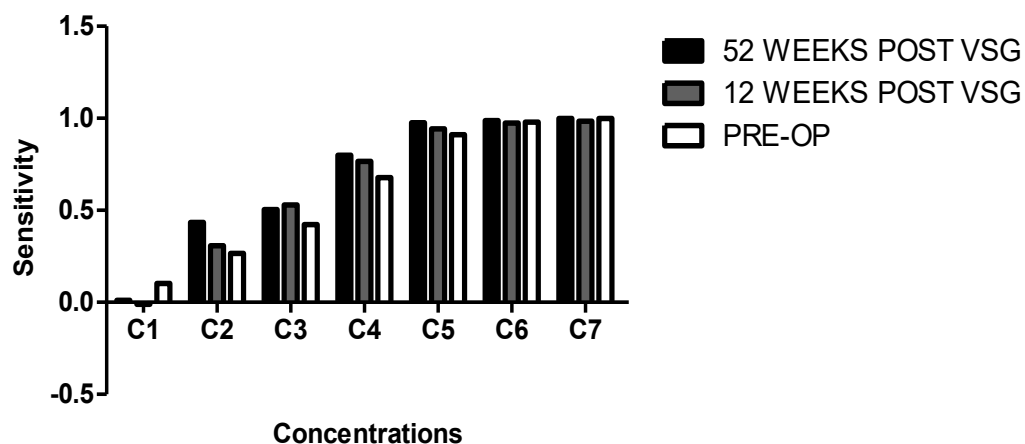
The 2-way repeated measures ANOVA used to study the comparison between groups (VSG vs. Control) and within Group comparisons to examine the Time effect (pre-op vs post-op) on the variables (Table 4.3-2). A post hoc effect of Time was illustrated within each group, according to the Time x Group interaction effect (Table 4.3-3). The EC50s showed no differences neither between groups nor according to time effect, No interaction Group x Time was seen (Figure 4.3.2-1). The Overall repeated measures ANOVA: Group $F(1,22)=1.3$, $p=0.27$, Time $F(1,22)=0.5$, $p=0.50$, Group x Time $F(1,22)=0.3$, $p=0.57$. A two-way repeated measures ANOVA was used in the VSG group to study the effect of time (pre-op vs. post-op) and the effect on concentrations of sucrose. There was a significant difference between concentrations $F(1,12)=95.8$, $p \leq 0.0001$, but no differences between pre and postoperative visits $F(1,12)=1.06$, $p=0.35$, and no interaction between concentrations and Time for visits, $F(1,12)=0.58$, $p=0.86$ (Figure 4.3.2-2).

Figure 4.3.2-1 Comparison between groups (VSG vs. Control) and within group to examine time effect on EC50s



Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs post-op) on EC50s showing no effects.

Figure 4.3.2-2 Comparison between concentrations and within visits (pre/post VSG) to examine time effect on Concentrations



Comparison between Concentrations and Time for visits (pre-op vs. post-op) in the VSG group (only) showed: significant differences between Concentrations $P \leq 0.0001$, no differences between visits $P = 0.35$, with no interaction between Concentrations and Time for visits $P = 0.86$.

Table 4.3-2 Two Way ANOVA Results

Two Way ANOVA results for Participant characteristics at baseline and 12 weeks. A summary of their response to sweet tastant after Vertical Sleeve Gastrectomy (VSG). Results are expressed as mean +/- SEM or median (interquartile range) depending on normality distribution.

	CONTROLS		SLEEVE		ANOVA					
	PRE	POST	PRE	POST	GROUP		TIME		GROUP X TIME	
Number	10	10	14	14	F ^a	P ^b	F ^a	P ^b	F ^a	P ^b
Participant Characteristics										
Age (years)	15.1±0.6	N/A	15.2±0.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Height (m)	1.68±0.03	1.68±0.03	1.66±0.02	1.66±0.02	0.18	0.66	N/A	N/A	N/A	N/A
Weight (kg)	88.4±6.2	90.1±9.1	138.9±5.2	101.8±7.7	14.5	*≤0.001	8.6	*0.008	10.3	*0.004
BMI (kg/m ²)	32.0±2.0	32.2±3.1	50.8±1.7	36.7±2.6	23.0	*≤0.001	8.2	*0.009	8.8	*0.007
Tested sucrose taste detection thresholds										
EC50s	-2.0±0.3	-2.0±0.1	-1.7±0.2	-1.9±0.1	1.3	0.27	0.50	0.50	0.3	0.57

Data presented as mean ± SEM

F^a (1, 22) for all ANOVA results.

P^b values for repeated measures ANOVA with Group as between subject factor and Time as within subject factor.

Table 4.3-3 Post hoc effects of Time within groups

Post-hoc Bonferroni significant differences test with Two Way ANOVA results for participant characteristics at baseline and 12 weeks. A summary of response to sweet tastant after Vertical Sleeve Gastrectomy (VSG). Results are expressed as mean +/- SEM or median (interquartile range) depending on normality distribution Post hoc effects of Time within each group, according to the Time x Group interaction effect.

	CONTROL VS. SLEEVE AT BASELINE		CONTROL VS. SLEEVE AT 12 weeks		CONTROL BASELINE VS. 12 weeks		SLEEVE BASELINE VS. 12 weeks	
	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value
Participant Characteristics								
Age (years)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Height (m)	0.02±0.04	0.7	0.02±0.04	0.7	N/A	N/A	N/A	N/A
Weight (kg)	-50.5±8.1	*≤0.001	-11.7±11.9	0.333	1.7±9.2	0.85	37.1±7.8	*≤0.001
BMI (kg/m ²)	-18.8±2.6	*≤0.001	-4.5±4.1	0.27	0.2±3.7	0.95	14.1±3.1	*≤0.001
Tested sucrose taste detection thresholds								
EC50s	-0.3±0.4	0.38	-0.1±0.1	0.28	0.02±0.3	0.94	0.2±0.2	0.34

4.4 Discussion

This study showed that VSG did not have an effect on the detection threshold for sucrose in adolescent patients. This is in contrast to the findings in adults after RYGB where an increase in sensitivity of sucrose have been detection (381). These results suggest that VSG might not fundamentally shift the sensory domain of taste, but food preference changes may instead be related to other factors such as conditioned avoidance.

This study utilised the method of constant stimuli, in which sucrose solutions were presented randomly and performance was assessed across a set of concentrations allowing for derivation of a psychometric function (381). Moreover, adolescent subjects obtained feedback by receiving tokens for correct responses and losing tokens for incorrect responses, which appeared to maintain subjects' vigilance and motivation in this "game-like competitive setting". The advantage of this technique is that it can also be used to measure taste sensitivity in animal models (385). Despite the fat mass loss, reduction in total body weight, and maintenance of weight loss observed after the VSG, changes in taste sensitivity were not observed. Using the same methodology, this data on sucrose detection threshold after VSG in adolescents are different to an existing data relating to adult patients undergoing RYGB (381). The change in taste detection thresholds for sucrose after RYGB remain controversial (585), but most of the available evidence are consistent with our previous findings (381). Scruggs et al. reported a trend for sucrose detection and recognition thresholds to decrease after RYGB (524). The concentration at which the subjects could correctly identify the characteristic taste quality of the stimulus was considered the recognition threshold. This technique, however, only stimulates a limited number of taste buds. Burge et al. used a staircase method of stimulus presentation and found that sucrose recognition thresholds also decreased after RYGB (523). These current results therefore suggest that adolescents after VSG behave in similar ways to some adult patients after RYGB.

There are reasons other than potential changes in the sensory nature, or unconditioned hedonic value of sweets, as to why patients would avoid some sugary or fatty foods and fluids (e.g. learning from post-ingestive consequences, nutritional counseling, or both (269;271;275;368;518;586;587). The study was limited as it did not have an adult or RYGB control group and therefore it cannot directly compare the results of this and the previously published study in adults after RYGB. In this study only 14 subjects were studied after VSG, but did not observe even a trend for a reduction in sucrose thresholds at either 12 or 52 weeks after VSG, suggesting that it studied a sufficient number of subjects to avoid a type II statistical error. The non-operated obese group did not receive any intervention and they were not studied at 1 year. Their only function was to ensure that the test used in this study provided the same results in subjects that were weight stable, even if they were tested on two different occasions. This was important to establish as the non-surgical subjects may have learnt how to do the test and this in itself may have altered the results.

In conclusion, VSG surgery did not decrease the taste detection to sucrose thus there was no increased sensitivity to sweets in the surgical group at either 12 or 52 weeks after VSG. Collectively, these results, along with previous modest changes observed from RYGB studies, highlight that changes in taste-driven motivated behaviour to sucrose after both VSG and RYGB may depend less on changes in the sensory domain of taste and relate more to learning. Therefore, studies examining conditioned taste avoidance, as a potential mechanism underlying the changes in food preferences after VSG, are eagerly awaited.

CHAPTER 5

**VERTICAL SLEEVE GASTRECTOMY IN OBESE
ADOLESCENTS REDUCES THE APPETITIVE REWARD
VALUE OF A SWEET AND FATTY REINFORCER IN A
PROGRESSIVE RATIO TASK**

5.1 Introduction

Childhood obesity is defined as a patients being above the 95th percentile for BMI. This serious public health and medical problems is rapid increasing worldwide (588). Obesity at this age represents one of the most challenging diseases to treat even within a multidisciplinary setting and if treated is started at an early age (58). A healthy lifestyle including a balanced diet and regular physical activity is crucial in the prevention of obesity but offers limited benefit for its treatment in the long term (589). Dieting can reduce body weight, but most patients regain the weight they have lost (259). Vertical sleeve gastrectomy (VSG) is an effective weight loss option in adults with long term benefits (229;562). The largest series of VSG in children and adolescents was performed at King Saud University Hospitals, Riyadh, Saudi Arabia, and reported the outcomes of 291 patients aged between 5 and 21 years. Successful weight loss and resolution of co-morbidities both occur within the first 2 years after surgery and continue for 5 years, but longer-term data are needed to better understand what happens as these patients mature into adulthood (236;237).

Anecdotal evidence from clinical practice and evidence from rodent models of VSG suggest a reduction in wanting of foods high in sugar and fat (529). Seeley et al showed that VSG in rats not only reduced total caloric intake, but also the proportion of dietary fat, with a shift to preferring lower caloric-density foods. These observations were consistent with findings using a progressive-ratio task (PRT) and conditioned taste aversion paradigm after VSG in rats(529). When food choice was compared between two anatomically different bariatric procedures (VSG and RYGB) in rats, there were very little difference in macronutrient intake (529). Roux-en-Y Gastric Bypass (RYGB) in humans lead to reduced motivation to ingest foods high in sugar and fat (264;369-371). However, there are no previous studies on VSG in adults or adolescents. In this study, the aim was to determine changes in the motivational reward value of a candy high in sugar and fat after VSG in

adolescents. To address this question the progressive ratio schedule of reinforcement was used as an operant task in a similar way Hodos did 50 years ago in animals (528).

5.2 Methods

This was a prospective study of obese adolescents eligible for bariatric surgery (BMI ≥ 40 kg/m² without comorbidity, or ≥ 35 kg/m² with comorbidity). Patients were under the care of the multidisciplinary obesity clinic for children and underwent VSG at King Saud University (KSU) in Riyadh, Saudi Arabia. The control group included overweight/obese adolescents who were recruited from the community and did not have an intervention, but were studied twice (10-12 weeks) to confirm the stability of the PRT and exclude *learning* as a confounder. Written, informed consent was obtained from all the subjects. The study was approved by the Ethics Committee at KKHU (Reference E 12-740). During the progressive ratio task, the subject performs a certain number of responses to obtain a reinforcer (i.e. reward). After delivery of each reward, the response requirement progressively increases until it is so great, the subject stops responding. This point is defined as the breakpoint. The number of responses “in the last completed ratio” indicates the reward value of the reinforcer and this task is a pure assessment of appetitive responsiveness driven by the stimulus properties of the reinforcer, such as its taste. Obese adolescents undergoing VSG and the non-surgical control group were instructed to have their usual breakfast until they felt “comfortably full” before starting the test. Testing occurred 2-3 hours after breakfast in a quiet room within the clinical research facility. Room temperature was maintained at 21°C. Participants were blinded to the study hypothesis, given exactly the same verbal and written instruction and specifically informed that there were no right or wrong responses to the task.

A power point presentation in Arabic that explained the Progressive Ratio Task (PRT) program provided instructions. Subjects rated their hunger, fullness and desire to eat immediately prior to the test starting, using a horizontal 100 mm Visual Analogue Scale (VAS) with the anchors “not at all” and “extremely” on either end (Appendix 14).

Subjects were placed in front of a computer screen and a plate of 20 chocolate candies (M&M[®] crispy candies, Mars UK Limited, Slough UK), each one containing approximately 4 kcal (energy contribution: 43.7% sugars, 44.1% fat) (Appendix 14). The following prompt appeared on the screen: “You can earn food by clicking on the mouse button. Click as much or as little as you like. When you no longer want to continue, press the spacebar to stop the session”. Upon completion of each ratio a message box appeared on the screen: “You have earned food. Enjoy your reward and after you have swallowed it completely you may click on OK to continue with the programme.” After ingesting the reward, the subjects then pressed the OK button in the message box only if they wished to progress to the next ratio in order to obtain another chocolate candy (Appendix 14). The starting ratio was 10 clicks with a geometric increment of 2 (i.e. 10, 20, 40, 80 etc.). This progression schedule was chosen based on previous experiments within this research group, at Imperial College London, UK (386). The instructor ensured that all participants understood the experiment, then left the room and subjects were left on their own to complete the task. The instructor was not present during the task to reduce any potential influence on the behavioural responses of the participant (386). When the effort of repeatedly pressing the mouse button was perceived to be greater than the reward value of the chocolate candy, subjects pressed on the space bar to terminate the session indicating the breakpoint was reached (Appendix 14). No food or fluid was offered after termination. The same numbers of chocolate candies (n=20) were presented to all participants. The number of candies left after completion of the experiment was subtracted from 20 to give the total number consumed. This was correlated with the number of completed ratios from the computer software to ensure participants followed the instructions reliably. Patients due to have VSG underwent testing two

weeks pre-operatively and 12 and 52 weeks post-operatively, whereas the control group tested on two occasions 8-12 weeks apart.

The sample size was calculated to detect an effect size of VSG of 0.85 standard deviations (SD) from the mean VAS rating. With 15 patients in each group this was predicted to permit greater than 90% power to detecting significant differences at the $p < 0.05$ level, using two tailed tests. The effects of sleeve gastrectomy on the study's outcomes have never been examined before. Therefore, the effect size used in the power calculation was informed by similar experiments on patients after RYGB using the same behavioural testing methods at Imperial College London.

Comparisons between and within groups were made using the Mann-Witney and Wilcoxon matched pairs test respectively. One-way ANOVA, within the surgical group was performed using repeated measures, Benferoni and the Friedman test respectively. Correlations were made using the Spearman non-parametric test, but the graphs include a parametric linear regression curve for visual comparison. The patient characteristic data were normally distributed and thus t-tests and ANOVA were used for within and between group comparisons for age and BMI, whilst gender comparisons were made with Fisher's exact test. Results are expressed either as mean $\pm$ SEM or median (interquartile range). GraphPad Prism[®] version 5 was used for statistical comparisons and/or SPSS[®] v22 for the Two Way ANOVA data analysis. Statistical power and study size calculations were based on our previously published data (386).

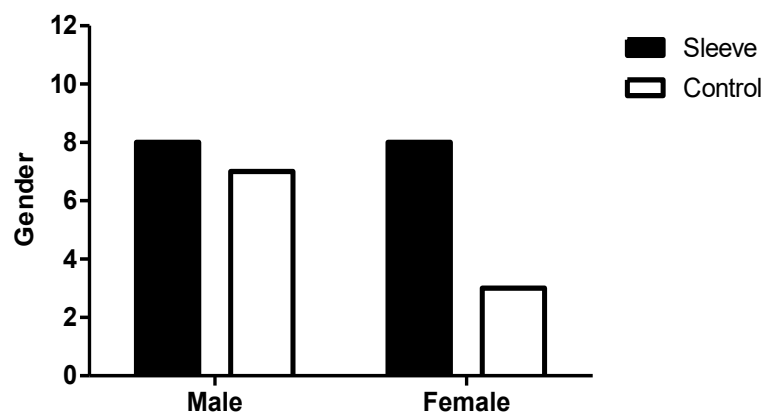
5.3 Results

5.3.1 One Way ANOVA Statistical Analysis

Table 5.3-1 shows the demographic characteristics of the participants. All eligible non-surgical participants were recruited and completed the study (n=10). In the surgical group 21 eligible patients were recruited (Figure 5.3.1-1, Figure 5.3.1-2), four patients chose not to complete the study and one

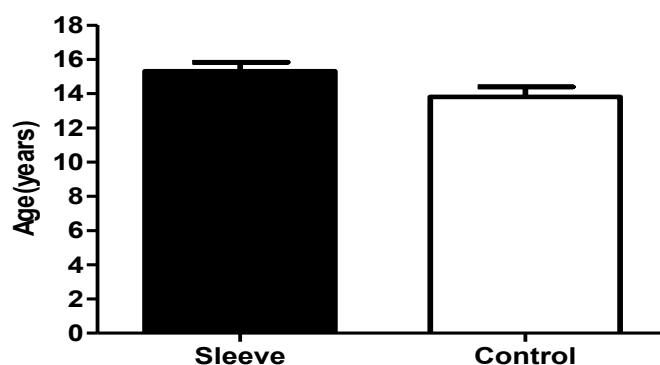
was excluded because of problems with his teeth as he couldn't tolerate the sweets. Data from completers are reported (Figure 5.3.1-3). The age of VSG was 15.3 ± 0.5 and the control group 13.8 ± 0.6 . There was no bodyweight change in the control group between the two sessions. The BMI decreased in the VSG group as compared to pre-surgery, from 49.7 ± 1.6 to 40.2 ± 1.7 and $31.4 \pm 1.0 \text{ kg/m}^2$ at 12 weeks and 52 weeks respectively. There were no discrepancies between the numbers of reinforcers actually consumed (counted after the session) and the number predicted to have been consumed based on the software results for either the patient or control groups (Figure 5.3.1-4).

Figure 5.3.1-1 Gender distribution in between the groups, VSG vs. Control



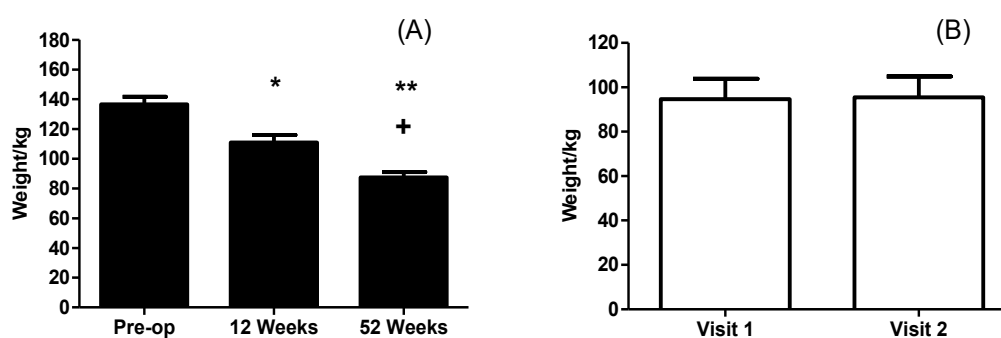
Graph plots the distribution of both male and female in between the groups, VSG vs. Control.

Figure 5.3.1-2 Matching Age for both groups, VSG vs. Control



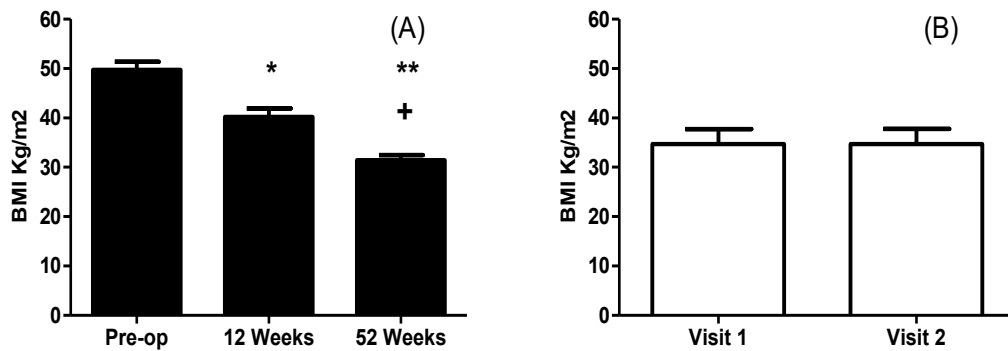
Graph plots the matching age for both groups, VSG vs. Control, they are matching.

Figure 5.3.1-3 Change in Weight pre/post VSG



Graph plots the changes in Weight through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit, +52 weeks significantly decreased as compared to 12 weeks. (B) Control groups no changes between the two visits.

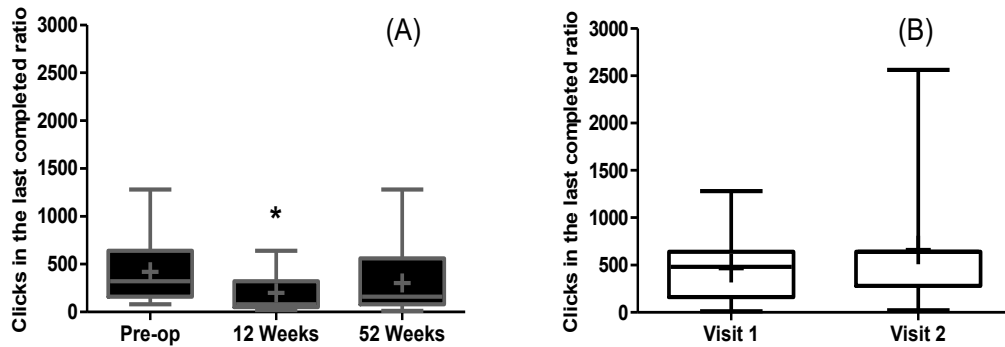
Figure 5.3.1-4 Change in BMI pre/post VSG



Graph plots the changes in BMI through all three interval visits, baseline, 12 and 52 weeks post VSG. (A) * 12 weeks, and ** 52 weeks are significantly decreased as compared to pre-op visit, +52 weeks significantly decreased as compared to 12 weeks. (B) Control groups no changes between the two visits.

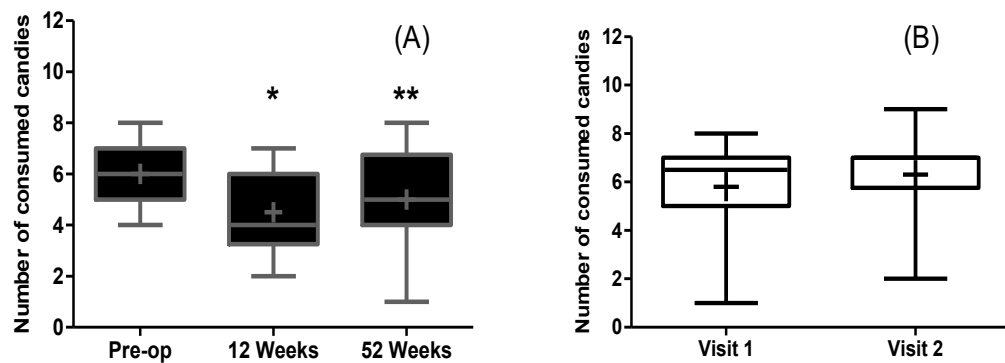
Breakpoints as assessed by the number of mouse clicks in the last completed ratio of the test did not differ in the control group between the two sessions and there was a significant correlation between the breakpoints for sessions 1 and 2 for the control subjects (Figure 5.3.1-5). There was no difference in breakpoints between the control group and obese group at baseline. However, there was more than 50% reduction in the median breakpoint of the VSG group at 12 weeks after surgery, which was maintained at 52 weeks (Figure 5.3.1-5). This was also the case for the median rewards (Figure 5.3.1-6). In addition, the postoperative decrease in weight correlated significantly with the decrease in breakpoint at 12 weeks (Figure 5.3.1-7, Figure 5.3.1-8). Hunger ratings did not change, whilst nausea ratings significantly increased in the VSG group at 12 weeks compared to pre-operatively (Figure 5.3.1-9).

Figure 5.3.1-5 Change in Clicks in the last completed ratio pre/post VSG



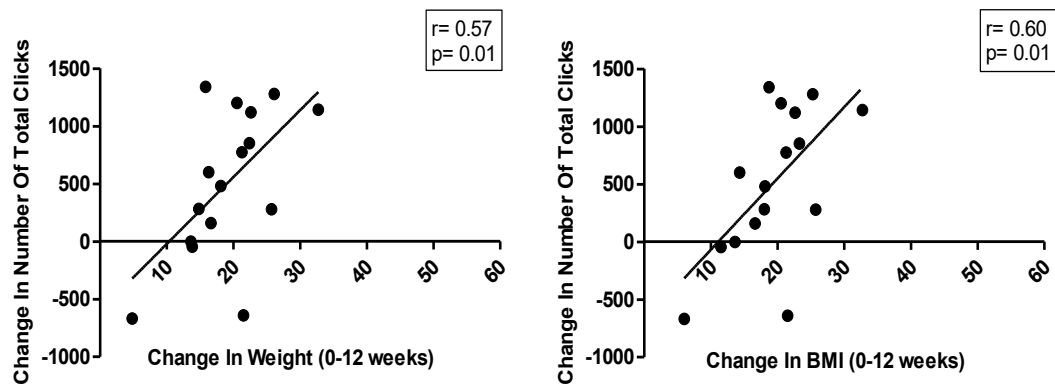
Box plot of breakpoint (i.e. Clicks in the last completed ratio) for M&M® crispies. The median is the gray/black line inside the box. * 12 weeks is significantly reduced as compared to pre-op visit.

Figure 5.3.1-6 Change in Number of consumed candies pre/post VSG



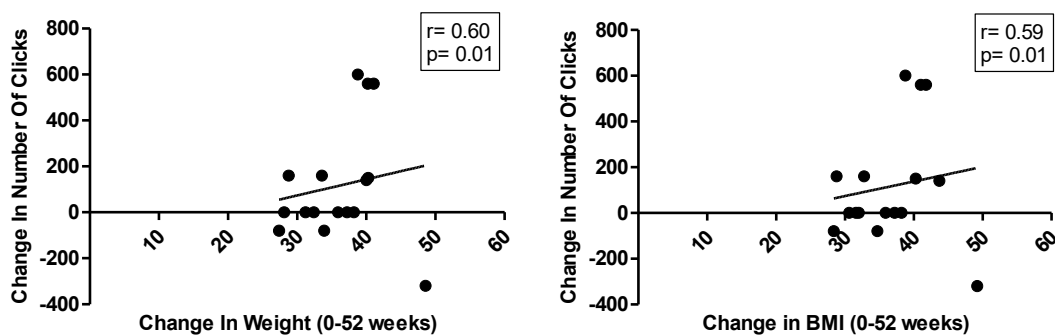
Box plot of the total Number of rewards for M&M® crispies. The median is the gray/black line inside the box. * 12 weeks is significantly reduced as compared to pre-op visit, ** 52 weeks is significantly reduced as compared to pre-op visit.

Figure 5.3.1-7 Correlation between change in Weight and BMI to examine the change in Total Clicks at 12 weeks



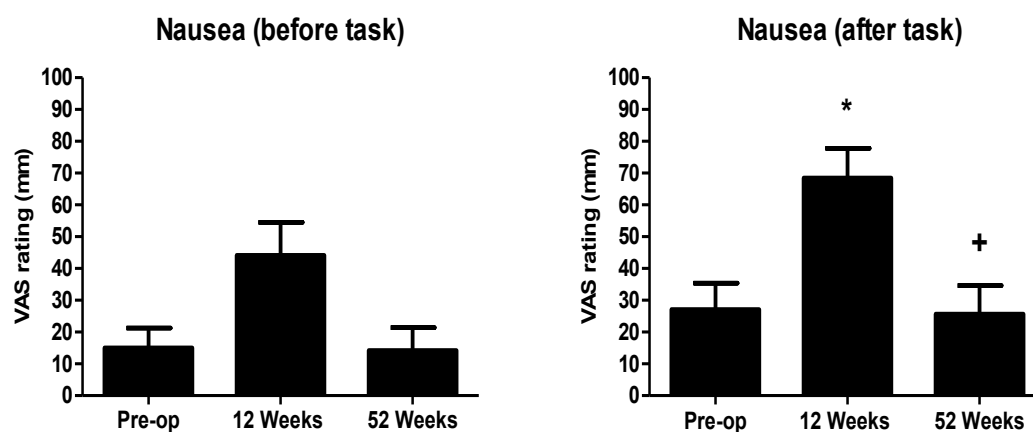
The postoperative decrease in Weight and BMI in patients correlated with the decrease in breakpoint for M&M® crispies (chocolate) at 12 weeks.

Figure 5.3.1-8 Correlation between change in Weight and BMI to examine the change in Total Clicks at 52 weeks



The postoperative decrease in Weight and BMI in patients correlated with the decrease in breakpoint for M&M® crispies (chocolate) at 52 weeks.

Figure 5.3.1-9 Change in Nausea (before and after task) pre/post VSG



Graph plots the changes in Nausea levels in VAS before and after the experiment session through all three interval visits, baseline, 12 and 52 weeks post VSG. (B)*12 weeks is significantly increased as compared to pre-op visit, +52 weeks is significantly reduced as compared to 12 weeks visit. (A) No significant changes.

Table 5.3-1 One Way ANOVA Results

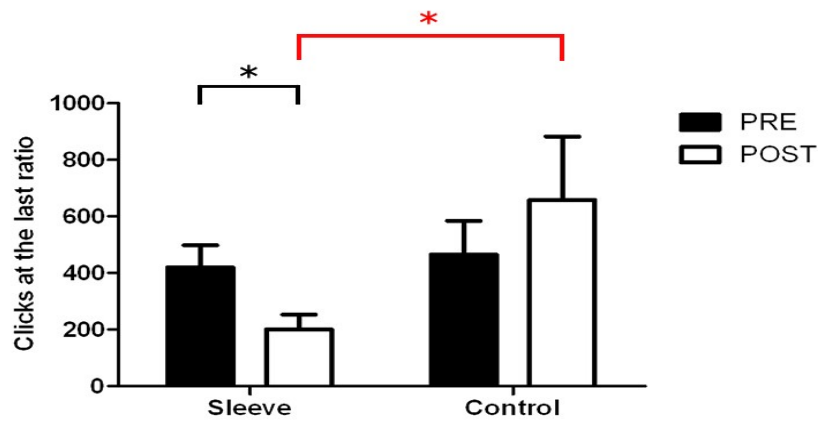
Participant characteristics at baseline and summary of responses at the progressive ratio task (PRT) and visual analogue scale ratings (VAS) at baseline and follow up. Patients were tested 12, and 52 weeks after vertical sleeve gastrectomy (VSG), whilst comparator participants were tested 8-12 weeks apart. Results are expressed as mean $\pm$ SEM or median (interquartile range) depending on normality distribution.

	VSG	VSG 12 weeks post-op (N=16)	VSG 52 weeks post-op (N=16)	P value within VSG group	Control Visit 1 (N=10)	Control Visit 2 (N=10)	P value within Control group	P value between groups at baseline
Participant characteristics								
Gender (M/F)	8/8	N/A	N/A	N/A	7/3	N/A	N/A	1.00
Age (years)	15.3 $\pm$ 0.5	N/A	N/A	N/A	13.8 $\pm$ 0.6	N/A	N/A	0.07
BMI (kg/m ²)	49.7 $\pm$ 1.6	40.2 $\pm$ 1.7	31.4 $\pm$ 1.0	*$\leq$0.0001	34.7 $\pm$ 3.0	34.7 $\pm$ 3.0	1.00	*$\leq$0.01
Responses at the PRT								
Clicks in last completed ratio	320(160-640)	80(50-32)	160(80-560)	*$\leq$0.01	480(160-640)	640(280-640)	0.17	0.87
Total rewards earned	6(5-7)	4(3-6)	5(4-7)	*0.002	6(5-7)	7(6-7)	0.12	0.87
Visual Analogue Scale ratings								
Hunger pre-test (cm)	33.8 $\pm$ 7.4	34.0 $\pm$ 9.1	30.5 $\pm$ 7.5	0.94	28.0 $\pm$ 7.2	35.2 $\pm$ 8.0	0.24	0.60
Fullness pre-test (cm)	60.3 $\pm$ 7.0	56.7 $\pm$ 9.4	69.1 $\pm$ 6.5	0.54	49.7 $\pm$ 9.2	58.6 $\pm$ 9.6	0.33	0.36
"Wanting" pre-test (cm)	55.1 $\pm$ 8.1	33.1 $\pm$ 7.8	43.4 $\pm$ 7.9	0.09	44.0 $\pm$ 5.9	52.4 $\pm$ 6.6	0.24	0.34
Nausea pre-test (cm)	15.0 $\pm$ 6.3	44.1 $\pm$ 10.3	14.2 $\pm$ 7.2	*0.03	10.8 $\pm$ 8.1	16.0 $\pm$ 10.4	0.65	0.69
Hunger post-test	28.8 $\pm$ 6.9	34.1 $\pm$ 10.8	16.3 $\pm$ 5.4	0.26	25.1 $\pm$ 8.9	30.3 $\pm$ 9.3	0.58	0.75
"Sweetness" post-test (cm)	69.7 $\pm$ 7.9	59.2 $\pm$ 9.1	77.4 $\pm$ 6.3	0.15	67.5 $\pm$ 10.9	76.4 $\pm$ 6.9	0.28	0.87
"Creaminess" post-test (cm)	58.9 $\pm$ 7.0	61.2 $\pm$ 8.1	62.8 $\pm$ 7.2	0.93	58.8 $\pm$ 8.5	60.8 $\pm$ 8.4	0.73	0.99
"Liking" post-test (cm)	61.9 $\pm$ 9.8	47.1 $\pm$ 9.3	61.3 $\pm$ 9.2	0.39	63.0 $\pm$ 10.7	73.1 $\pm$ 9.1	0.18	0.94
Nausea post-test (cm)	27.0 $\pm$ 8.4	68.4 $\pm$ 9.4	25.6 $\pm$ 9.0	*0.0006	10.0 $\pm$ 7.1	7.7 $\pm$ 6.5	0.18	0.17

5.3.2 Two Way ANOVA Statistical Analysis

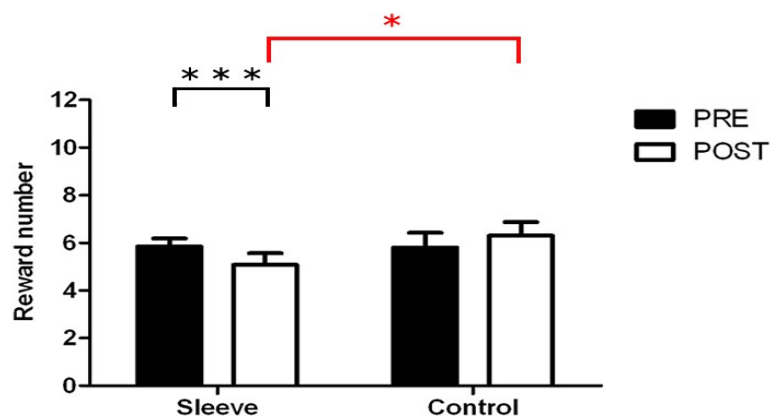
The 2-way repeated measures ANOVA used to study the comparison between groups (VSG vs. Control) and within Group comparisons to examine the Time effect (pre-op vs post-op) on the variables (Table 5.3-2). Post hoc effects of Time were illustrated within each group, according to the Time x Group interaction effect (Table 5.3-3). Changes in the appetitive behaviour was studied through PRT test that shows changes in the clicks in last completed ratio (breakpoints) that signifies changes in the reward value after surgery within the VSG adolescent patients as compared to the control group. Clicks in last completed ratio (breakpoints) were significantly decreased after 12 weeks in patients post VSG. The Overall repeated measures ANOVA: Group $F(1,24)=2.9$, $p=0.10$, Time $F(1,24)=0.03$, $p=0.85$, Group x Time $F(1,24)=8.5$, $*p=0.008$. ($*p=0.02$) with post-hoc Bonferroni significant differences test (Figure 5.3.2-1). An interaction between Group and Time have also presented that the Total Rewards earned have reduced in number accordingly. Overall repeated measures ANOVA: No differences were shown between groups (VSG vs control), $F(1,24)=1.8$, $p=0.18$, as well as no differences between visits (Time), $F(1,24)=2.8$, $p=0.10$, but a significant interaction between Group and Time for visits was seen, $F(1,24)$, $*p=0.003$. ($*p \leq 0.001$) with post-hoc Bonferroni significant differences test (Figure 5.3.2-2). Nausea post-test measures at the VAS showed changes in patients post VSG. Overall repeated measures ANOVA: Group $F(1,24)=14.3$, $*p \leq 0.001$, Time $F(1,24)=7.5$, $*p \leq 0.01$, Group x Time $F(1,24)=9.4$, $*p \leq 0.005$. ($*p \leq 0.001$) with post-hoc Bonferroni significant differences test (Figure 5.3.2-4).

Figure 5.3.2-1 Comparison between groups (VSG vs. Control) and within group to examine time effect on Clicks at the last completed ratio



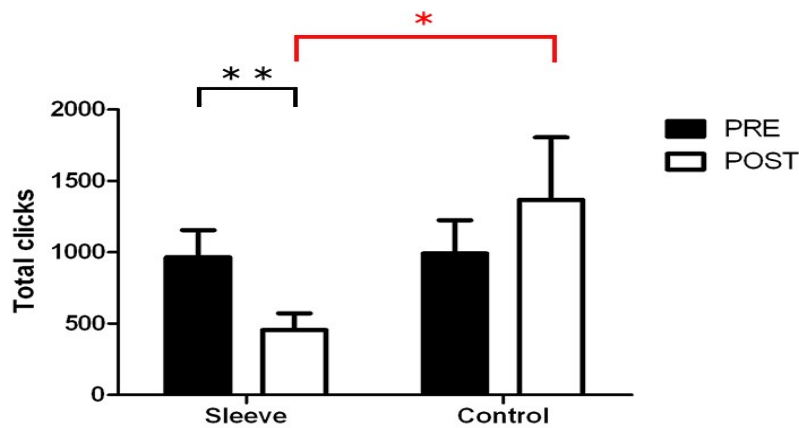
Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs post-op) on clicks at the last ratio, showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Figure 5.3.2-2 Comparison between groups (VSG vs. Control) and within group to examine time effect on Reward number



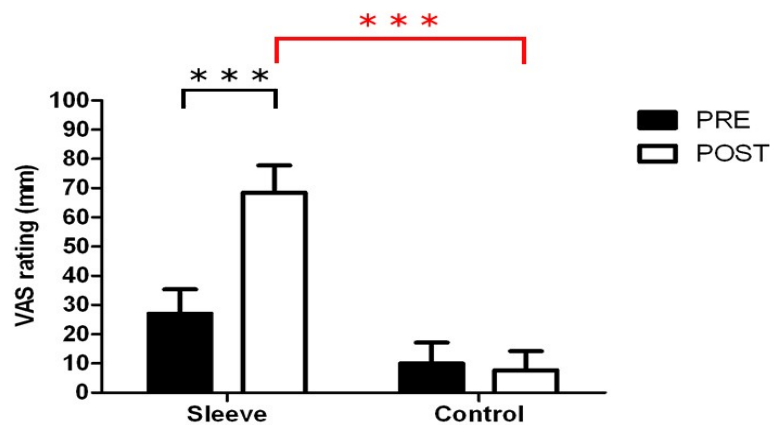
Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs post-op) on reward number (number of consumed candies), showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Figure 5.3.2-3 Comparison between groups (VSG vs. Control) and within group to examine time effect on Total Clicks



Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs post-op) on total clicks, showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Figure 5.3.2-4 Comparison between groups (VSG vs. Control) and within group to examine time effect (pre-op vs post-op) on Nausea post test



Comparison between groups (VSG vs Control) and within group comparisons to examine the time effect (pre-op vs post-op) on Nausea post test, showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Table 5.3-2 Two Way ANOVA Results

Two Way ANOVA results for Participant characteristics at baseline and 12 weeks. A summary of their response to sweet/fat tastant using the (PRT) after Vertical Sleeve Gastrectomy (VSG). Results are expressed as mean +/- SEM or median (interquartile range) depending on normality distribution.

	CONTROLS		SLEEVE		ANOVA					
	PRE	POST	PRE	POST	GROUP		TIME		GROUP X TIME	
Number	10	10	16	16	F ^a	P ^b	F ^a	P ^b	F ^a	P ^b
Participant characteristics										
Age (years)	13.8±0.6	N/A	15.3±0.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Height (m)	1.66±0.03	1.66±0.073	1.66±0.12	1.67±0.12	N/A	N/A	N/A	N/A	N/A	N/A
Weight (kg)	94.7±7.6	95.4±7.8	136.6±6.0	110.9±6.1	8.8	*0.007	88.0	*≤0.001	98.5	*≤0.001
BMI (kg/m2)	34.7±2.4	34.7±2.5	49.7±1.9	40.2±1.98	10.8	*0.003	95.3	*≤0.001	95.3	*≤0.001
Responses at the PRT										
Clicks in last completed ratio	465±107	658±146	420±84	201±115	2.9	0.10	0.03	0.85	8.5	*0.008
Total rewards earned	5.8±0.5	6.3±0.6	6.0±0.4	4.5±0.4.0	1.8	0.18	2.8	0.10	11.3	*0.003
Total Clicks	992±237	1369±292	966±187	456±230	2.3	0.13	0.2	0.65	9.3	*0.005
Visual Analogue Scale pre-test										
Hunger pre-test (cm)	28±8.6	35.2±10.3	33.8±6.8	34±8.2	0.06	0.80	0.2	0.65	0.17	0.67
Fullness pre-test (cm)	49.7±9.0	58.6±11.0	60.3±7.1	56.7±8.8	0.2	0.64	0.09	0.76	0.5	0.48
“Wanting” pre-test (cm)	44.0±8.9	52.4±8.8	55.1±7.0	33.1±7.0	0.2	0.62	0.8	0.37	4.1	0.055
Nausea pre-test (cm)	10.8±8.0	16.0±12.1	15.0±6.4	44.1±9.6	3.4	0.07	3.1	0.09	1.5	0.23
Visual Analogue Scale post-test										
Hunger post-test	25.1±8.8	30.3±12.2	28.8±7.0	35.1±9.6	0.11	0.74	0.45	0.50	0.001	0.99
“Sweetness” post-test (cm)	67.5±10.4	76.4±10	69.7±8.2	59.2±8.0	0.43	0.51	0.02	0.90	2.3	0.14
“Creaminess” post-test (cm)	58.8±8.8	60.8±9.5	58.9±7.0	61.2±7.5	0.001	0.98	0.1	0.74	0.001	0.98
“Liking” post-test (cm)	63.0±11.8	73.1±10.8	61.9±9.3	47.1±8.6	1.35	0.25	0.08	0.78	2.2	0.15
Nausea post-test (cm)	10.0±9.5	7.7±10.2	27.0±7.5	68.4±8.1	14.29	*≤0.001	7.49	*≤0.01	9.35	*0.005

Data presented as mean ± SEM

F^a (1,24) for all ANOVA results.

P^b values for repeated measures ANOVA with Group as between subject factor and Time as within subject factor.

Table 5.3-3 Post hoc effects of Time within groups

Post-hoc Bonferroni significant differences test with Two Way ANOVA results for participant characteristics at baseline and 12 weeks. A summary of response to sweet/fat tastant after Vertical Sleeve Gastrectomy (VSG). Results are expressed as mean +/- SEM or median (interquartile range) depending on normality distribution

	CONTROL VS. SLEEVE AT BASELINE		CONTROL VS. SLEEVE AT 12 weeks		CONTROL BASELINE VS. 12 weeks		SLEEVE BASELINE VS. 12 weeks	
	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value
Participant Characteristics								
Age (years)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Height (m)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weight (kg)	-41.9±9.6	*≤0.001	-15.5±9.9	0.13	0.7±2.1	0.73	25.7±1.7	*≤0.001
BMI (kg/m2)	-15.0±3.1	*≤0.001	-5.5±3.2	0.097	0.01±0.8	1.0	9.5±0.6	*≤0.001
Responses At The PRT								
Clicks in last completed ratio	45±137	0.74	457±186	*0.02	193±110.7	0.09	218.8±87.5	*0.02
Total rewards earned	-0.2±0.6	0.74	1.8±0.7	*0.02	0.5±0.5	0.29	1.5±0.4	*≤0.001
Total Clicks	26±303	0.93	913±372	*0.02	377±227	0.11	510±180.1	*0.009
Visual Analogue Scale Pre-Test								
Hunger pre-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fullness pre-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
"Wanting" pre-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nausea pre-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Visual Analogue Scale Post-Test								
Hunger post-test	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
"Sweetness" post-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	CONTROL VS. SLEEVE AT BASELINE		CONTROL VS. SLEEVE AT 12 weeks		CONTROL BASELINE VS. 12 weeks		SLEEVE BASELINE VS. 12 weeks	
	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value
"Creaminess" post-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
"Liking" post-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nausea post-test (cm)	-17.0±12.0	0.17	-60.7±13.0	*≤0.001	2.3±11.2	0.83	41.4±8.9	*≤0.001

5.4 Discussion

This study has shown that the appetitive reward value of a tastant high in sugar and fat decreased after VSG surgery in adolescents. Our data is consistent with the changes shown in rodents after VSG (529) and in adult patients after RYGB (386). Our method built on the literature involving the use of PRT in humans (386;590-596).

One of the key merits of the PRT is that the assessment is based on the actual behaviour of the subject and is not burdened by interpretive limitations associated with verbal report or scaling procedures. Our study answered the question of how hard adolescents were willing to work for a given reinforcer that was high in sugar and fat. Our model employed simple computer software, in which participants actually tasted the reinforcer during the task rather than postponing the consumption to the end. Thus, appetitive responsiveness was determined directly by the orosensory properties (e.g. taste) of the reward and did not rely on the association between a stimulus like a token, money or images with the reward. Completion of the schedule was not dependent on computer skills or the completion of an intellectually demanding task. In an attempt to minimise post-ingestive effects, reinforcers were of minimal volume and calories. It is this property that makes the PRT ideal for studying changes in appetitive responsiveness after VSG so that ingestion of a food reward may not lead to premature satiation or satiety signals from the small bowel and interfere with its orally based evaluation. Participants were briefed about the experiment by the investigator, who was absent from the room during the task itself, in order to minimise bias in the responses. The above methodological features differentiate our paradigm from others used in humans including reports on RYGB (269;275;279;362;373). Analytical taste and/or post-ingestive effects contribute to these effects on preference, which are often perceived as changing to more “healthy choices” (269;271;275;279;362;368;373;518;586).

In our previous study changes in breakpoints observed following RYGB matches the reports of reduced preference. As was noted within that study, the assessment was quantified on the basis of measurement of the objective behaviour of the subject. Our findings following VSG in adolescents are consistent with both those from the human study of RYGB (386) and also those in animals following VSG (529). Using the same paradigm in rats after RYGB, we were not able to show a change in breakpoint (597). This does raise the question of whether, despite best efforts, patients may still “behave” in a specific way to “please” the investigator, a problem that is not seen in rats. Accepting the limitations of the VAS, and whilst the increase in nausea did not correlate with the reduction in breakpoint, the higher nausea ratings after VSG may reflect the presence of negative visceral signals contributing to conditioned taste *avoidance*; the subject gradually learns that a small amount of high fat and sugary food are still rewarding after surgery, but a larger amount may have to be avoided to prevent negative consequences. This is akin to patients with lactose intolerance still enjoying a small amount of milk, but learning to avoid large amounts of milk. Our results do not suggest that conditioned taste *aversion* took place, as all the subjects continued to exert some level of effort to achieve at least two candies 12 and 52 weeks after VSG. If a true aversion had been present, they would likely not have exerted any effort in pursuit of the tastant. The breakpoints of the VSG and control group were similar at baseline, which is consistent with our previous findings in adults (386). It is thus tempting to speculate that obese adolescents and adults will not necessarily work harder than normal weight subjects for high fat and sugary foods if the environment can be structured in such a way as to require increasing effort to attain these obesogenic foods. This argument may support portion control as an effective measure to reduce the incidence of childhood obesity.

Our study has certain limitations. The control group was lighter than the VSG group and was not studied one year after inclusion in the study. However, it was reassuring that the control group appetitive responses to the task remained stable over an 8-12 week period. Peri-operative dietary

advice may have prejudiced the patients against the consumption of food high in sugar and fat. Therefore, it's not possible to entirely exclude the possibility that subjects' responses were influenced by their own cognitive expectations regarding how they thought they were expected to behave toward the reinforcer. However, this is an unavoidable limitation of any assessment of food preference and hedonics in an experimental setting. It should be stressed that the subjects were clearly instructed that there was no right or wrong performance. Indeed, the small volumes of rewards ingested coupled with the simple response requirement associated with the task hopefully reduced the influence of cognitive factors on the outcome. It is almost impossible to objectively assess a subject's true intent, but instead of just relying on verbal or written ratings, it is at least possible to directly measure a subject's behaviour; indeed in the context of this experiment, the behavioural outcomes correlated remarkably well with the changes in BMI and are consistent with the available reports in the literature regarding changes in food preferences and hedonics after VSG (529;577).

It was beyond the scope of this study to investigate the mediators of the change in appetitive behaviour after VSG. It is noteworthy that the responses of post-prandial anorexigenic gut hormones (glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY) are enhanced after both the VSG and RYGB, despite the anatomical differences between them. The administration of GLP-1 and PYY has been shown not only to increase fullness and decrease caloric intake, but also to reduce behavioural and brain reward system responses to energy-dense foods or cues in humans and rodents (598). Future work is necessary to investigate the role of gut hormones, alongside altered nutrient sensing in the gut and other physiological signals, in the reduction of the reward value of energy-dense food after both procedures.

In conclusion, using the progressive ratio task this study demonstrated a reduction in appetitive behaviour for a palatable energy-dense reward following VSG in obese adolescents. Direct

measurement of appetitive behaviour is therefore both possible and informative in humans after VSG. It is now possible to study the underlying mechanisms responsible for this change, both in animal and human experiments. By understanding the mechanisms by which VSG decreases consumption of high-calorie fat and sweet foods and alters taste responses, new and existing surgical and non-surgical therapies can be developed to reproduce these processes and so encourage safe and effective weight loss for adolescents.

CHAPTER 6

**CHANGES IN “FACIAL EXPRESSIONS” IN OBESE
ADOLESCENTS WHEN REACTING TO TASTANT
STIMULANTS AFTER VERTICAL SLEEVE GASTRECTOMY**

6.1 Introduction

The prevalence of overweight and obesity has increased considerably in children and adolescents in developed countries. In 2013, 23·8% and 22·6% of boys and girls were considered overweight or obese. The prevalence of overweight and obesity has also increased among the same age group in developing countries in 2013, from 8·1% to 12·9% among boys and from 8·4% to 13·4% among girls (18). The Middle Eastern countries of Egypt, Libya, Iran, Turkey, and the Gulf region, including Saudi Arabia (SA), are examples of countries with some of the highest prevalence rates of obesity in old and young people (18;25;26). In SA, cultural factors may contribute heavily to the extensive problem. Saudi Arabia, covers around two-thirds of the Arabian Peninsula, and has a population of 30.8 million people, of whom 20.7 million are Saudis (44). According to a 2007 survey, 37% of the population are ≤ 15 years (45). The prevalence of overweight and obesity among young people ≤ 20 years old in Saudi Arabia has been estimated at 19.0% and 23.3% respectively. More than 50% of children in SA between 14 and 18 years had weight above the 85th percentile in year 2010 (49).

The best strategies and policies to control the epidemic of obesity have not been established yet (83). Diet and exercise are examples from several strategies for obesity treatment, both considered useful for losing weight in adults with moderate obesity. However, it appears that even losing weight with these methods, most persons with obesity do not maintain weight loss for long periods (84). VSG is emerging as a standalone procedure (222). From 1997 to 2003, the volume of adolescent bariatric surgery done in the United States was projected to have increased 5-fold, from 51 to 282 (226). Alongside this, data from a global survey have shown an increase in the use of VSG, from 0% of all procedures in 2003, to 5.4% in 2008 (170). Al Qahtani has published recently updated data relating to 226 paediatric patients, concluding that VSG resulted in successful short-term weight loss. Furthermore, 90.3% of comorbidities remitted or improved, 64.9% of which did so within the first 3 postoperative months. Although no further improvement or remission was observed beyond

2 years, there was no recurrence up to 3 years in patients who were seen in follow-up. The loss to follow-up, across each of 3 years of follow-up, was 4.2%, 7.6%, and 15.3%, respectively (237). Long-term data are needed for better understanding and evaluation of weight loss maintenance and maturation to adulthood (236;237). The most recent study to date was published by Al Sabah et al. with a total of 135 adolescent patients, who underwent VSG, followed up for an average of twenty months. The patients had a median age of 19 years (range 12-21) and a mean BMI of 48.5 kg/m². The %EWL at 2 years for males and females was 84 and 77 %, respectively. All patients with type 2 diabetes mellitus and 75 % of those with hypertension presented complete resolution at 2 years (238). Human obesity and weight gain have been linked to an elevated preference for both sweet and/or high-fat diet (355;356). An increased appetite for sweet or high-fat foods may explain why people with obesity readily gain and subsequently regain body weight (357;358). For example; these two energy rich components account for around 60% of the daily energy content of the typical American diet (22% from sugar and 37% from fats) For example, these two energy rich components account for around 60% of the daily energy content of the typical diet in the United States (22% from sugar and 37% from fats) (468). Discrepancy exists between the published studies that have investigated whether people with obesity have a higher preference for sweet-tasting foods, or have a different threshold for sweetness compared to the non-obese (469-478). The common view about fat is comparable to that for sugar; it is presumed that obese people show a greater liking for high-fat foods (357;486;487). In these studies, mixing fat with other dietary components was of special interest for researchers. Drewnowski and his colleagues conducted a study that used dairy products (with diverse sugar and fat content) to study more about this mixture between fat and sugar and how palatable it might be. Their data showed that women with obesity preferred a higher ratio of fat to sweet than men, and that a mixture of sweet and fat offered a particularly palatable taste (357). In a study by Bartoshuk et al. data were collected using the general labeled magnitude scale (gLMS).

This group illustrated those individuals with obesity experience, not only a greater preference for sweet and high-fat foods in the first place, but also that their perception of sweetness is weaker than individuals who do not have obesity. Perhaps this will open the 'synergism' between fat and sweet sensations to a greater degree of understanding, and an expression of taste loss in the obese will offer researchers new ways to think concerning the increased liking for fat in the obese population. In sum, the research team have concluded that liking of both fat and sweet rises in line with increasing BMI (471). It is not clear yet in the literature, why liking for sweet and fat tastes increase as BMI increases. It is established, though, that the relationship between orosensory experience and post-ingestive effects of sweet and fat foods contributes to liking (489) and, indeed that the hedonism associated with palatable foods is considered a significant factor in the increased prevalence of obesity. Taste detection thresholds are only one basic aspect of taste function and have been shown to vary as a function of genetics, pharmacological treatment, and neural manipulations (515). Taste hedonics and alterations in reward responses have not been fully explored as a potential mechanism for the development of obesity. The search for the neural basis of any behavioural or sensory process must begin with a clear articulation of the principles of function. With this in mind, there is ample evidence that the sense of taste serves several functions that can be experimentally classified into at least three general domains (379):

1-Stimulus identification is the detection or discrimination of sensory signals arising from taste cell activation in the oral cavity.

2-Ingestive motivation refers to processes that promote or discourage ingestion of foods and fluids on the basis of taste input. Ingestive motivation can be further divided into two functional subclasses: Appetitive behaviour ("wanting") and consummatory behaviour ("liking")

3-Digestive preparation refers to physiological reflexes that fall into a general class referred to as cephalic phase responses, which are internal physiological events triggered by stimulus contact with any sensory receptor of the head (516). Bariatric surgery could be exerting its effects on food selection and preference through any one of these functional domains; sensory-discriminative (or stimulus identification), hedonic (or ingestive motivation) and the physiological (or digestive preparation) domains (379;380). Altered taste function in humans can be measured through various means.

Sensory domain

Behaviour has previously been measured directly, using a constant stimuli method to determine detection thresholds on the sensory domain of sweet taste in patients who had undergone gastric bypass surgery for obesity (385). This technique has also been used to measure taste sensitivity in animal models (385) After RYGB, patients' sucrose detection threshold decreased (523) and sensitivity increased, to this sweet stimulus, suggesting that surgery has consequences on the sensory processing of taste signals generated by sucrose (381).

Reward domain: appetitive behaviour

Although there are suggestions in animal models that the rewarding and inhibiting properties of sweet and fat stimuli may change after RYGB (263;381-385), very little work has been undertaken in humans to determine whether there are any changes in the hedonic domain of taste function after other weight loss surgery, such as VSG. This has been addressed by the use of the progressive ratio schedule of reinforcement, an operant task first developed by Hodos 50 years ago (528) for use in animals. In our previous study we demonstrated that the change in breakpoints, observed following RYGB, matches anecdotal patient reports of reduced preference.

However, as noted within that study, the assessment was actually quantified on the basis of measurement of the objective behaviour of the subject, rather than reported behaviours (386).

Reward domain: consummatory behaviour

Another objective way to study human feeding behaviour, is taste reactivity as measured by “the involuntary, minute movements of the face in response to a stimulus” (531). These can be studied to enable an impression of the emotional state of an individual as a consequence of the applied stimulus. Taste reactivity studies using facial expression which looked at infants, apes, new world monkeys and rats concluded that there were two major reaction patterns seen: the positive, hedonic reaction - typically to sweet taste - was characterised by lip smacking, tongue protrusion and even a smile, while the negative (aversive) reaction to bitter taste involved grimacing, retracting of the lips, wrinkling of the nose and retraction of the head away from the food source. Other tastes, such as salt or sour, were found to produce responses with intermediate reactions between those described above (532-536). The use of taste reactivity to study the ingestive motivation, consummatory behaviour of taste in adult humans has been less well investigated. Previous work has shown that adults do demonstrate facial reactivity, with some promising results (533;535;537;538), though it was considered that adults may not be as accurate as a consequence of socialisation and voluntary or higher control (535;539). Taste reactivity has not previously been used for the study of consummatory reward in obese patients. The consequence of VSG on the complex central reward circuits has not been studied before. By understanding the mechanisms by which VSG decreases consumption of high-calorie fat and sweet foods and alters taste responses, new surgical and non-surgical therapies could be developed that reproduce these processes and so encourage safe and effective weight loss. The aim of this study is to assess changes in consummatory behaviour after VSG in adolescents, as compared to the non-operated control group, by determining changes in “facial expressions” in adolescents when reacting to tastant stimulants after VSG.

To study and evaluate oromotor reflexes as related to consummatory behaviour pre surgery, and after 10 days and 12 weeks, in adolescents after VSG.

6.2 Methods

Within this pilot study, five non-obese control subjects were examined twice, while the seven obese sleeve subjects were examined before surgery and twice (10 days and 12 weeks) after VSG. Written, informed consent was obtained from all the subjects. The study was approved by the Ethics Committee at KKUH (Reference E 13-932). Participants were instructed to come to the Clinic Research Centre CRC fasting overnight for the test. The same investigator was available throughout the experimental period and explained the experiment, provided the visual analogue sheets and assured the confidentiality of the recordings. A commercial chocolate milkshake Galaxy® was used (50 ml, 52 kcal), the camera was prepared to start recording, and the patient were asked to complete a VAS of hunger and fullness just before and after the experiment (Appendix 15). The investigator ensured that the milkshakes flowed directly and accurately into the subjects' mouths by hanging the milkshake in a giving set bag from a 1.5-2 meters stand and thus using gravity to deliver a rate of 25mL/minute (Appendix 15). Then simple written instructions were provided on paper detailing: "You will be filmed for two minutes whilst the milkshake is poured into your mouth. There are no right or wrong answers in this experiment. You will not put on weight as a result of this task. You can stop the infusion at any point, subjects were told." A bowl was placed next to the subject to expel any potential excess milk shake into if they wish. The subject was also shown how to turn the infusion off and how to remove the straw from their mouth, in case they wished to do so during any part of the study. The investigator asked if the subjects had any questions. If not, the record button on the camera was pressed, the infusion began and the investigator left the room. After two minutes the investigator re-entered the room to stop the experiment. The patient was then asked to

complete the second VAS. Facial Expression Food Preference Rating Scale, Like vs. Dislike of Standardized Tastent was created and used based on a selection of the action Units (AUs) from the Facial Action Coding System (FACS) system (Appendix 15). The AUs that show most consistency in the literature with regard to the positive or negative affective value (599).

The sample size was calculated to detect an effect size of VSG of 0.85 standard deviations (SD) from the mean VAS rating. With 15 patients in each group this was predicted to permit greater than 90% power to detecting significant differences at the $p < 0.05$ level, using two tailed tests. The effects of sleeve gastrectomy on the study's outcomes have never been examined before. Therefore, the effect size used in the power calculation was informed by similar experiments on patients after RYGB using the same behavioural testing methods at Imperial College London.

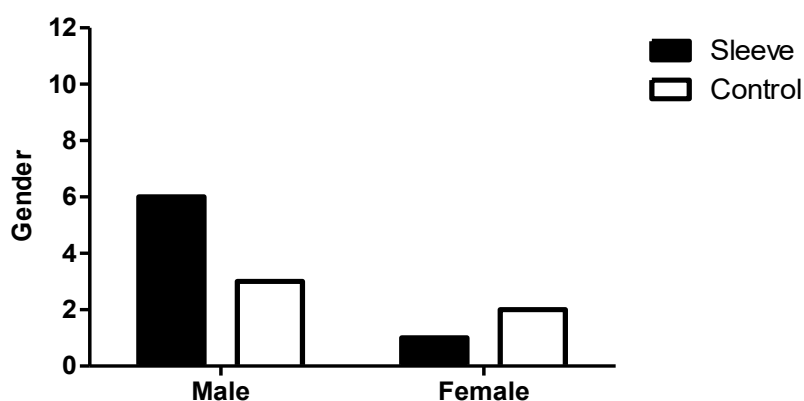
Comparisons between and within groups were made using the Mann-Witney and Wilcoxon matched pairs test respectively. One-way ANOVA, within the surgical group was performed using repeated measures, Benferoni and the Friedman test respectively. Correlations were made using the Spearman non-parametric test, but the graphs include a parametric linear regression curve for visual comparison. The patient characteristic data were normally distributed and thus t-tests and ANOVA were used for within and between group comparisons for age and BMI, whilst gender comparisons were made with Fisher's exact test. Results are expressed either as mean $\pm$ SEM or median (interquartile range). GraphPad Prism[®] version 5 was used for statistical comparisons, and/or SPSS[®] v22 for the Two Way ANOVA data analysis.

6.3 Results

6.3.1 One Way ANOVA Statistical Analysis

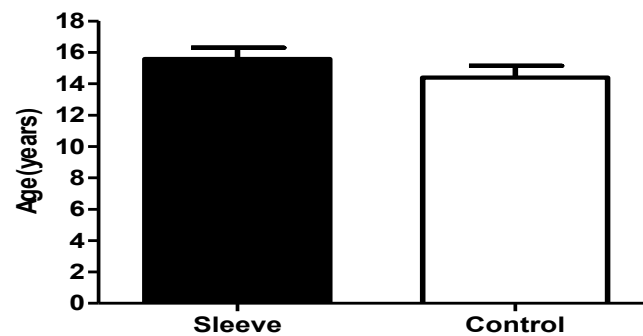
At this pilot study, Table 6.3-1 shows the demographics of the participants. In the surgical group 7 eligible patients were recruited (Figure 6.3.1-1). Data from completers are reported for both surgical and non-surgical group. The age of the surgical group was 15.6 ± 0.7 years, and for the non-surgical group 14.4 ± 0.7 years ($p = 0.3$) (Figure 6.3.1-2). BMI was 52.5 ± 2.4 kg/m² and 28.8 ± 2.0 kg/m², respectively ($p=0.003$) (Figure 6.3.1-3). There was no bodyweight change in the non-surgical group between the two sessions, but the VSG group reduced their weight from 144 ± 8.9 kg, to 132.1 ± 8.5 kg and 113.3 ± 7.1 kg at 10 days and 12 weeks ($p=0.066$) (Figure 6.3.1-4).

Figure 6.3.1-1 Gender distribution in between the groups, VSG vs. Control



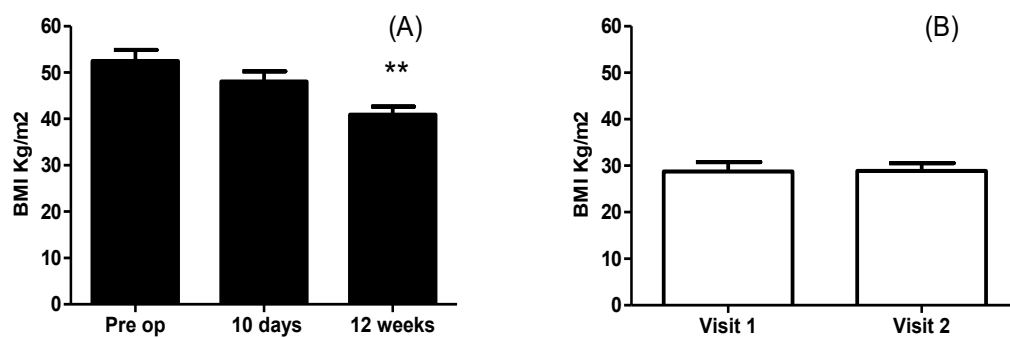
Graph plots the distribution of both male and female in between the groups, VSG vs. Control.

Figure 6.3.1-2 Matching Age for both groups, VSG vs. Control



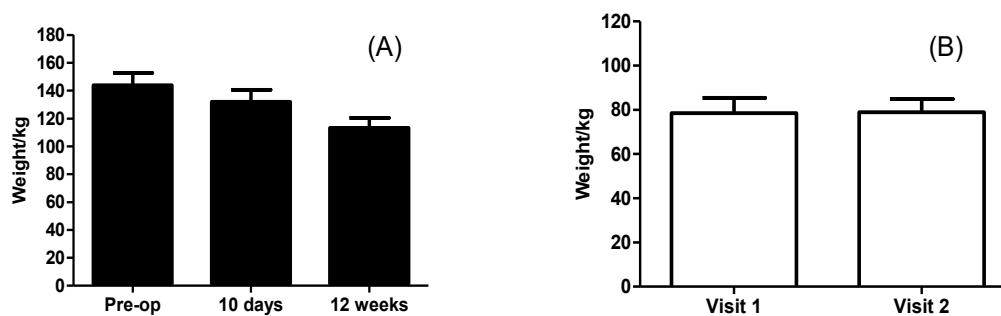
Graph plots the matching age for both groups, VSG vs. Control, they are matching.

Figure 6.3.1-3 Change in BMI pre/post VSG



Graph plots the changes in BMI through all three interval visits, baseline, 10 days and 12 weeks post VSG. (A) ** 12 weeks is significantly decreased as compared to pre-op visit. (B) Control groups no changes between the two visits.

Figure 6.3.1-4 Change in Weight pre/post VS

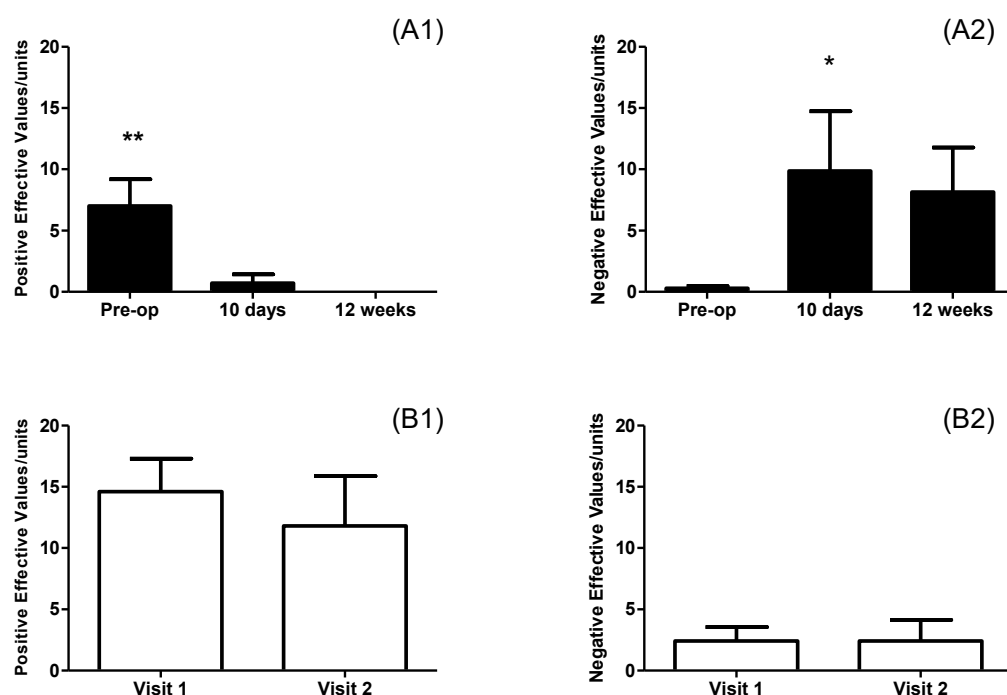


Graph plots the changes in Weight through all three interval visits, baseline, 10 days and 12 weeks post VSG. (A) No significant decrease was shown as compared to pre-op visit. (B) Control groups no changes between the two visits.

VAS did not change among both the surgical and non-surgical subjects through all visits (Table 6.3-1).

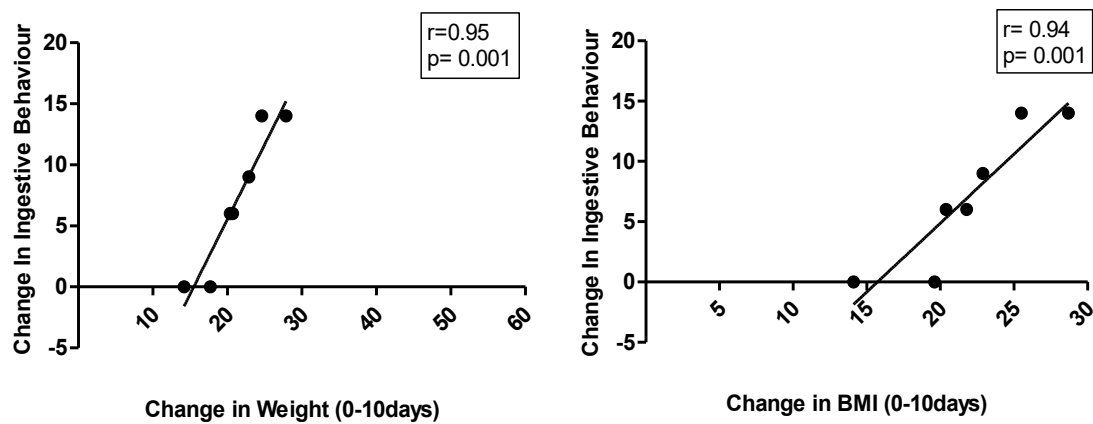
The video analysis results are shown in (Table 6.3-1, Figure 6.3.1-5) for both negative and positive effective values (NEV, PEV). A significant increase was observed in NEV in the surgical group, from 0.3 ± 0.2 units at baseline (pre-op), to 9.9 ± 4.9 units and 8.1 ± 3.6 unit ($p=0.02$), 10 days and 12 weeks post-operatively, respectively. PEV reduced significantly, from 7.0 ± 2.2 unit at baseline, to 0.7 ± 0.7 unit and zero units at 10 days and 12 weeks respectively ($p=0.03$). The non-surgical group showed no changes in either NEV or PEV (Figure 6.3.1-5).

Figure 6.3.1-5 Change in Positive Effective Behaviour and Negative Effective Behaviour pre/post VSG



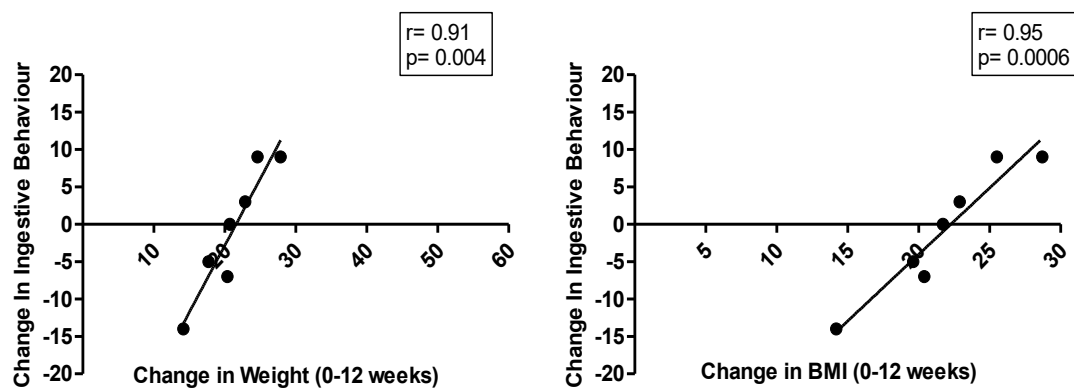
(A1) Changes in the Positive Effective Values (PEV) at baseline visit (pre-op), 10 days, and 12 post VSG ($p=0.03$). (A2) Changes in the Negative Effective Values (NEV) at baseline visit (pre-op), 10 days and 12 post VSG ($p=0.02$). *Denotes a significant change from baseline to 10 days. (B1, B2) Control groups no changes between the two visits.

Figure 6.3.1-6 Correlation between change in Weight and BMI to examine the change in Ingestive Behaviour at 10 days



The postoperative decrease in Weight and BMI in patients correlated with the changes (decrease) in ingestive behaviour at 10 days post-op.

Figure 6.3.1-7 Correlation between change in Weight and BMI to examine the change in Ingestive Behaviour at 12 weeks



The postoperative decrease in Weight and BMI in patients correlated with the changes (decrease) in ingestive behaviour at 12 weeks post-op.

Table 6.3-1 One Way ANOVA Results

Participant characteristics at baseline, 12 and 52 weeks. A summary of response to sweet/fat tastant using facial expressions after vertical sleeve gastrectomy (VSG). Results are expressed as mean +/- SEM or median (interquartile range) depending on normality distribution.

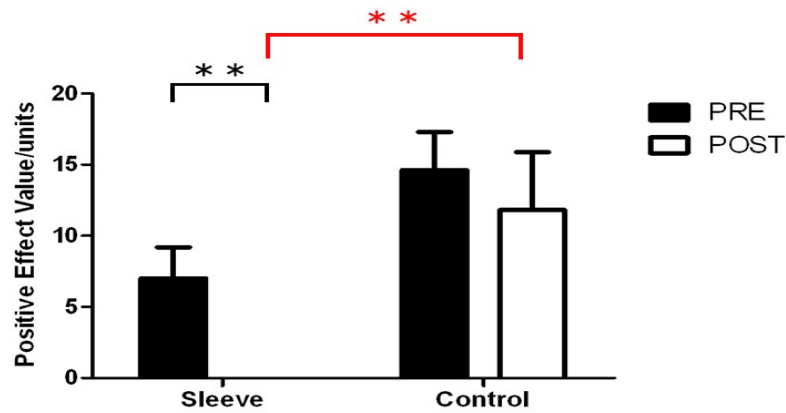
	VSG Pre-op (N=7)	VSG 10 days post-op (N=7)	VSG 12 weeks post-op (N=7)	P value within VSG group	Control Visit 1 (N=5)	Control Visit 2 (N=5)	P value within Control group	P value between groups at baseline
Participant characteristics								
Gender (M/F)	6/1	N/A	N/A	N/A	3/2	N/A	N/A	0.38
Age (years)	15.6±0.7	N/A	N/A	N/A	14.4±0.7	N/A	N/A	0.34
BMI (kg/m2)	52.5±2.4	48.1±2.2	40.9±1.8	*≤0.005	28.8±2.0	28.9±1.7	0.91	*0.003
Video Facial Expression Analysis Food Preference Behavior								
General Behavior	8.4±2.5	8.0±2.0	7.4±2.0	0.61	9.4±1.4	6.4±1.6	0.13	0.93
Negative Effective Value	0.3±0.2	9.9±4.9	8.1±3.6	*0.02	2.4±1.2	2.4±1.7	0.87	0.14
Positive Effective Value	7.0±2.2	0.7±0.7	0.0±0.0	*0.03	14.6±2.7	11.8±4.1	0.34	0.07
Behavior total raw score								
Visual Analogue Scale Ratings pre- test								
Hunger pre-test (cm)	53.0±9.3	62.7±14.8	45.1±10.6	0.55	51.2±21.1	66.4±6.8	1.0	1.0
Fullness pre-test (cm)	43.6±4.7	44.4±13.7	37.9±8.0	0.90	22.2±8.9	16.0±10.1	0.67	0.06
“Wanting” pre-test (cm)	32.7±15.0	56.3±14.9	41.7±17.0	0.72	51.6±14.7	53.0±9.8	1.0	0.59
Nausea pre-test (cm)	29±9.4	27.7±10.8	10.4±7.5	0.28	15.2±12.6	14.6±14.4	0.90	0.36

	VSG Pre-op (N=7)	VSG 10 days post-op (N=7)	VSG 12 weeks post-op (N=7)	P value within VSG group	Control Visit 1 (N=5)	Control Visit 2 (N=5)	P value within Control group	P value between groups at baseline
Visual Analogue Scale Ratings post-test								
Hunger post-test	44.9±11.1	22.7±6.5	29.9±9.1	0.31	50.0±16.7	57.0±12.5	0.67	0.9
“Sweetness” post-test (cm)	68.4±12.0	71.4±12.6	86.3±4.1	0.58	48.0±9.7	60.0±7.9	0.30	0.2
“Creaminess” post-test (cm)	39.0±11.4	55.4±9.5	66.3±5.6	0.24	59.2±6.4	65.8±8.4	0.91	0.3
“Liking” post-test (cm)	77.3±9.2	70.9±12.1	68.7±13.0	0.90	85.4±5.6	90.2±7.7	0.60	0.7
Nausea post-test (cm)	21.6±12.4	24.0±13.5	21.3±13.5	0.76	3.2±2.5	0.2±0.2	0.44	0.2

6.3.2 Two Way ANOVA Statistical Analysis

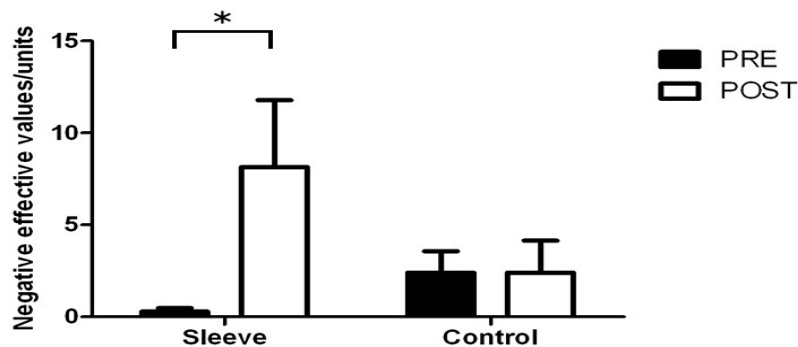
The two-way repeated measures ANOVA (Table 6.3-2, Figure 6.3.2-1) was used to study the comparison between groups (VSG vs. Control), and within group comparisons to examine the timing effect (pre-op vs. post-op) on the variables. Given our *a priori* hypothesis of enhanced effects of time (post-op vs. pre-op) in VSG group, Post hoc effects of time were illustrated within each group, irrespective of the Time x Group interaction effect (Table 6.3-3, Figure 6.3.2-2) The facial expression PEVs showed significant differences between groups, and also according to the time effect for visits. Nonetheless, no Time x Group interaction was seen. The overall repeated measures ANOVA: Group $F(1,10)=10.4$, $*p=0.009$, Time $F(1,10)=9.4$, $*p \leq 0.01$, Group x Time $F(1,10)=1.7$, $p=0.21$. ($*p=0.007$) with post-hoc Bonferroni significant differences test. Facial expression NEV did not show any difference, either between groups $F(1,10)=0.6$, $p=0.44$, or according to the effect of time, $F(1,10)=2.6$, $p=0.13$. No Group x Time interaction was seen $F(1,10)=1.7$, $p=0.21$. ($*p=0.03$) with *post-hoc* Bonferroni significant differences test. General Behaviour as response to the sweet/fat tastant in the Facial expression test for food preferences likes vs. dislikes did not change using the two-way ANOVA analysis. Group $F(1,10)=0.001$, $p=0.99$, no differences between visits $F(1,10)=1.1$, $p=0.32$, and no interaction between Group and Time for visits, $F(1,10)=0.3$, $p=0.61$.

Figure 6.3.2-1 Comparison between groups (VSG vs. Control) and within group to examine time effect on Positive Effective Behaviour



Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs. post-op) on Ingestive Behaviour (PEV), showing the effects of Time within each group, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Figure 6.3.2-2 Comparison between groups (VSG vs. Control) and within group to examine time effect on Negative Effective Behaviour



Comparison between groups (VSG vs. Control) and within group comparisons to examine the time effect (pre-op vs. post-op) on Negative Effective Behaviour (NEV), showing the effects of Time within each groups, according to the Time x Group interaction effect. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Table 6.3-2 Two Way ANOVA Results

Participant characteristics at baseline and 12 weeks. A summary of response to sweet/fat tastant using facial expressions after vertical sleeve gastrectomy (VSG). Results are expressed as mean +/- SEM or median (interquartile range) depending on normality distribution.

	CONTROLS		SLEEVE		ANOVA					
	PRE	POST	PRE	POST	GROUP		TIME		GROUP X TIME	
Number	5	5	7	7	F ^a	P ^b	F ^a	P ^b	F ^a	P ^b
Participant Characteristics										
Age (years)	14.4±0.7	N/A	15.6±0.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Height (m)	1.65±0.03	1.65±0.04	1.65±0.03	1.66±0.03	N/A	N/A	N/A	N/A	N/A	N/A
Weight (kg)	78.6±9.3	78.9±7.5	143.9±7.8	113.3±6.4	21.1	*≤0.001	53.8	*≤0.001	55.9	*≤0.001
BMI (kg/m ²)	28.8±2.5	28.9±1.9	52.5±2.1	40.9±1.6	39.5	*≤0.001	59.1	*≤0.001	60.4	*≤0.001
Video Facial Expression Analysis Food Preference Behavior										
General Behavior	9.4±2.5	6.4±2.1	8.4±2.1	7.4±1.8	0.001	0.99	1.1	0.32	0.3	0.61
Negative Effective Value	2.4±0.8	2.4±3.5	0.3±0.6	8.1±2.96	0.6	0.44	2.6	0.13	2.6	0.13
Positive Effective Value	14.6±2.6	11.8±2.6	7.0±2.2	0.001±2.2	10.4	*0.009	9.4	*≤0.01	1.7	0.21
Visual Analogue Scale pre-Test										
Hunger pre-test (cm)	51.2±15.8	66.4±10.6	53.0±13.4	45.1±9.0	0.6	0.44	0.09	0.77	0.8	0.38
Fullness pre-test (cm)	22.2±7.1	16.0±9.8	43.6±6.0	37.9±8.2	5.97	*0.04	0.8	0.40	0.001	0.97
“Wanting” pre-test (cm)	51.6±16.6	53.0±16.7	32.7±14.1	41.7±14.1	0.6	0.44	0.2	0.63	0.1	0.73
Nausea pre-test (cm)	15.2±11.8	14.6±11.4	29.0±10.0	10.4±9.6	0.1	0.73	2.6	0.13	2.3	0.16
Visual Analogue Scale post-Test										

	CONTROLS		SLEEVE		ANOVA					
	PRE	POST	PRE	POST	GROUP		TIME		GROUP X TIME	
Number	5	5	7	7	F ^a	P ^b	F ^a	P ^b	F ^a	P ^b
Hunger post-test	50.0±14.7	57.0±11.5	44.9±12.4	29.9±9.7	1.2	0.29	0.2	0.66	1.5	0.25
“Sweetness” post-test (cm)	48.0±12.6	60.0±6.3	68.4±10.6	86.3±5.3	5.0	*≤0.05	3.6	0.085	0.1	0.72
“Creaminess” post-test (cm)	59.2±11.2	65.8±7.4	39.0±9.5	66.3±6.3	1.3	0.28	3.5	0.09	1.3	0.27
“Liking” post-test (cm)	85.4±9.1	90.2±12.9	77.3±7.7	68.7±10.9	2.3	0.16	0.03	0.86	0.4	0.54
Nausea post-test (cm)	3.2±11.5	0.2±12.4	21.6±9.7	21.3±10.4	2.8	0.12	0.03	0.87	0.02	0.89

Data presented as mean ± SEM

F^a (1, 10) for all ANOVA results.

P^b values for repeated measures ANOVA with group as between subject factor and time as within subject factor.

Table 6.3-3 Post hoc effects of Time within groups

Post-hoc Bonferroni significant differences test with Two Way ANOVA results for participant characteristics at baseline and 12 weeks. A summary of response to sweet/fat tastant after using facial expressions Vertical Sleeve Gastrectomy (VSG). Results are expressed as mean +/- SEM or median (interquartile range) depending on normality distribution.

	CONTROL VS. SLEEVE AT BASELINE		CONTROL VS. SLEEVE AT 12 weeks		CONTROL BASELINE VS. 12 weeks		SLEEVE BASELINE VS. 12 weeks	
	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value
Participant Characteristics								
Age (years)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Height (m)	-0.003±0.05	0.95	-0.008±0.05	0.86	N/A	N/A	N/A	N/A
Weight (kg)	-65.3±12.1	*≤0.001	-34.4±9.9	*0.006	0.3±3.2	0.92	30.6±2.7	*≤0.001
BMI (kg/m ²)	-23.7±3.3	*≤0.001	-12.1±2.5	*≤0.001	0.06±1.1	0.95	11.5±0.96	*≤0.001
Video Facial Expression Analysis Food Preference Behaviour								
General Behaviour	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Negative Effective Value	2.1±0.99	0.059	-5.7±4.6	0.24	0.01± 3.7	1.0	7.9±3.1	*0.03
Positive Effective Value	7.6±3.5	0.052	11.8±3.4	*0.006	2.8±2.4	0.27	7.0±2.1	*0.007
Visual Analogue Scale Pre-Test								
Hunger pre-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fullness pre-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
“Wanting” pre-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nausea pre-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	CONTROL VS. SLEEVE AT BASELINE		CONTROL VS. SLEEVE AT 12 weeks		CONTROL BASELINE VS. 12 weeks		SLEEVE BASELINE VS. 12 weeks	
	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value	Mean Difference	P Value
Visual Analogue Scale Post-Test								
Hunger post-test	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
“Sweetness” post-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
“Creaminess” post-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
“Liking” post-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nausea post-test (cm)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

6.4 Discussion

This pilot study is the first study to focus on facial expressions in obese adolescent VSG patients in response to food stimuli. The aim was to investigate whether facial expressions represent a suitable and accurate measure, by which to quantify food preferences in adolescent obese patients before and after VSG. Although caution should be applied to the interpretation of the results because of the small number of subjects, this study delivers certain insights that might be valuable for researchers who are studying obese patients' food preference changes after bariatric surgery. This study used the facial expression method to assess changes in the consummatory behaviour relating to a single, specific food item after VSG surgery. The results indicate that negative facial expressions for disliked sweet/fat stimuli are more often encountered after VSG. Our hypothesis that negative expressions will increase, and positive expressions decrease for disliked stimuli, was confirmed. In addition, facial expressions remained unchanged across a similar test-retest interval in non-surgical control subjects.

Expressions that are evoked by foods, based on an emotion that is clearly food-related, include the expression of disgust (600). When a stimulus is liked (i.e. sweet solution), infants will smile, which is a sign of happiness. However, although the liked stimuli in our pilot study evoked an expression of happiness in the subject, it was difficult to detect and distinguish them from the neutral facial expressions. It has been suggested that, since the foods that humans consume and accept tend to result in mild positive reactions (601); it may be difficult to distinguish degrees of liking (food acceptance) based on facial expressions (599). Another group was able to conclude that facial expressions are suitable to measure dislike, but not suitable to measure several gradients of food acceptance in children aged 5–13 years. They felt that including drinks that are better-liked (possibly

milkshakes) than previously used juices and sweet solutions, might be preferable when studying positive facial expressions (599). Nevertheless, other studies indicate as well that the human system is much more responsive to potentially dangerous substances (disliked) than it is to safe, liked stimuli (602;603). One of the key merits of the task used here is that the assessment was based on the actual behaviour of the subject and was not burdened by some of the interpretive limitations associated with scaling procedures. Our study answered the question of whether an obese adolescent subject likes or dislikes the sweet/fat stimulus after VSG surgery. Our model comprised a simple piece of apparatus, which ensured that the milkshake flowed directly and securely into the subjects' mouths as described above. Thus, consummatory responsiveness was determined directly by the orosensory properties (e.g. taste) of the sweet/fat stimuli. Effort was made to minimise post-ingestive effects, and the reinforcer was of limited volume and calories.

In this study, large differences were observed in the expressiveness of the seven VSG adolescents' patients and the non-surgical group of five. Some were very expressive and others hardly showed any facial responses. To capture the more subtle changes in the face, it may be useful to apply electromyogram (EMG) measurements in future studies. EMG measurements or an automated scoring system, which can capture more subtle or humanly imperceptible changes in the face and would make the measurement of facial expressions more objective and more widely accessible as a research tool (604;605). It is unclear how much masking and control occurs in response to food stimuli. Since masking and control influence the objectivity of facial expressions as a tool for measuring food preferences, future research should examine how much masking and control is present at various ages and how much between-subject variation is present concerning masking and controlling expressions (599). The use of facial expressions to study the consummatory reward function of taste in human adults has been less well investigated. Previous work has shown that adults do demonstrate a degree of facial reactivity, with some promising results (533;535;537;538)

However, it was considered that they may not be as accurate owing to a combination of socialisation and voluntary or higher control (535;539).

Taste reactivity has not been used for the study of consummatory reward in obese adults as yet. The major limitation to the use of facial reactivity is the difficulty in interpretation of these often small and subtle movements (535). A few studies have used Facial Action Coding System (FACS) with trained interpreters (606). However, recently new face recognition software packages have been developed that enable the more objective assessment of facial reactivity and the duration of the facial reaction, providing a better overall feedback on the emotional state of the subject (e.g. FaceReader™). This technology is promising and could be further improved in terms of specificity, sensitivity and adapted to cultural and social facial reactivity differences (607). On the basis of the results of this pilot study VSG is implicated in changes in consummatory behaviour in adolescents, by determining changes in “facial expressions” when reacting to tastant stimulants. Additionally, facial expressions appear to be suitable to measure dislike, as well as various gradients of food acceptance in adolescents with obesity. Future studies with a larger number of VSG patients should be performed to confirm these results. The literature regarding bariatric surgery from human and animal experiments has broadly described reduced preference for refined sugars and fat, without pinpointing taste and/or post-ingestive effects as the cause for this perceived migration toward foods often considered more “healthy choices” (269;271;275;279;362;368;373;518;586).

CHAPTER 7

DISCUSSION

7.1 Discussion

7.1.1 Most important findings

In this study, no changes were demonstrated in taste threshold, but changes in appetitive and consummatory eating behaviour were apparent after VSG. Changes were related to food preference, eating behaviour and meal patterns after VSG in obese adolescents' patients.

7.1.2 Strength: Eating behaviour and meal pattern

7.1.2.1 Food preferences

The studies described in Chapter 3 demonstrate for the first time the powerful effect of VSG surgery in altering food choice in adolescents, particularly by decreasing fat intake. These data provide another parallel between the effects of VSG and RYGB, suggesting that these two anatomically-distinct procedures may share a common mechanism to induce their effects. Furthermore, this effect on food choice, along with many other effects of VSG and RYGB, is not shared with AGB, indicating that AGB is fundamentally different from the other two and does not fall into the category of metabolic surgery (529).

7.1.2.2 Eating behaviour and attitude of eating

Data in Chapter 3 also demonstrate that VSG changes eating behaviour and specifically leads to reduced meal size, meal duration and rate of eating when eating *ad libitum*. Emotional eating and unconditioned eating decreased postoperatively, while cognitive restraint increased. Possible mechanisms include changes in appetite regulatory hormones, leading to less hunger, which in turn may reduce eating rate and energy intake (292;293). Eating rate may also be reduced to attenuate the risk of dumping syndrome, which can occur when high glycaemic index carbohydrates rapidly reach the proximal small intestinal (608). Reports documenting gastric emptying following VSG are

inconsistent (461;462), and it is also unclear how often VSG is associated with symptoms of dumping syndrome, but a recent study suggested that symptoms of dumping syndrome occur in almost half of patients

6 weeks after VSG (572).

7.1.3 Strength: Taste detection

Using the same methodology, my data on sucrose detection threshold after VSG in adolescents were different to our previous data from adults after RYGB (381). The change in taste detection thresholds for sucrose after RYGB remain controversial (585), but most of the available evidence are consistent with our previous findings (381). Scruggs et al. reported a trend for sucrose detection and recognition thresholds to decrease after RYGB (524). The concentration at which the subjects could correctly identify the characteristic taste quality of the stimulus was considered the recognition threshold. This technique, however, only stimulates a limited number of taste buds. Burge et al. used a staircase method of stimulus presentation and found that sucrose recognition thresholds also decreased after RYGB (523). Taken together, these data suggest that RYGB has, if any, a small effect on the sensory domain of taste. Our results therefore suggest that adolescents after VSG behave in similar ways to some adult patients after RYGB. There are reasons other than potential changes in the sensory nature or unconditioned hedonic value of sweets as to why patients would avoid some sugary or fatty foods and fluids, e.g. learning from post-ingestive consequences and or nutritional counseling (269;271;275;368;518;586;587).

7.1.4 Strength: Appetitive behaviour

In this study I have shown that the appetitive reward value of a tastant high in sugar and fat decreased after VSG surgery in adolescents. My data is consistent with the changes shown in rodents after VSG (529) and in adult patients after RYGB (386). My method built on the literature involving

the use of PRT in humans (386;590-596). One of the crucial advantages of the task used here is that the assessment is based on the actual behaviour of the subject and is not loaded by some of the interpretive limitations associated with scaling procedures. Our study answered the question of how hard was an adolescent subject willing to work for a given reinforcer. The food reward system is a complex neural system that can be divided both anatomically and operationally into several components. One reasonable and important operational difference has been to distinguish hedonic “liking” from “wanting” and learning as proposed by Berridge and Robinson (609).

This differentiation is based on the simple fact that a food item that is liked is not essentially wanted at a given time, and that learning is needed to predict the reward value of a given food (610). Potential effects of bariatric surgery (RYGB and VSG), on brain areas involved in reward, cognitive, and emotional functions, contribute to the control of food intake, representing the expanded homeostatic system regulating energy balance. Changes in circulating hormones and metabolites, as well as changes in neuronal inputs from visceral afferents, may affect: (1) the processing of sensory information all along the specific input pathways, (2) reward computation in the mesocorticolimbic dopamine system, (3) emotional valence computation in the amygdala, (4) formation and modification of ‘food memories’ in the insular and prefrontal cortex and, (5) decision-making and executive control (611).

Looking for possible neural mechanisms that underlie changes in “wanting”, particularly changes in activation of components of the mesolimbic dopamine system, there is a growing literature base engaging functional magnetic resonance imaging, or fMRI. Specifically, fMRI studies from rodents show reduction in preference for sweet and fatty foods post RYGB or VSG. Correspondingly, while one recent study found RYGB patients to be less willing to work and exert effort for high-calorie food, there is no clear consensus about changes in the motivation to gain food rewards (“wanting”) and its

underlying mesolimbic dopamine system. Flow of information is hypothetically involved in the physiological and behavioural consequences of VSG and RYGB surgery. The primary surgical affront in the gut leads to progressive adaptive changes in structure (e.g., mucosal hypertrophy) and function (e.g., shift in microbiota composition, hormone release patterns, and bile-acid metabolism). These mutual changes signal to other organs, such as the liver, pancreas, adipose tissue, muscle, and brain, through either the circulatory or nervous system, and eventually lead to changes in energy intake, energy expenditure, and food choice. Alterations in signaling to the brain do not only affect food intake, but also autonomic nervous system and endocrine outflow back to the gut as well as to the other organs (577;611).

7.1.5 Strength: Consummatory behaviour

On the basis of my pilot study results, I demonstrated that VSG surgery made some changes in consummatory behaviour in adolescents, as compared to the pre-surgical phase, by determining direct measure changes in “facial expressions” in adolescents when reacting to tastant stimulants after VSG. Data also demonstrated that facial expressions are suitable to measure dislike, as well as various gradients of food acceptance in adolescent patients with obesity. The literature regarding bariatric surgery from human and animal experiments has broadly described the development of reduced food preference for refined sugars and fat, without pinpointing taste and/or post-ingestive effects as the cause for this change to more “healthy choices” (269;271;275;279;362;368;373;518;586). Studies from the literature designed to determine the neural component(s) accountable for these adaptive changes further propose that “liking” of not only high-fat, but also high-sucrose taste stimuli, is reduced post RYGB. However, whether this shift towards lower calorie-density sweet and fatty stimuli is due to changes in taste acuity or more central components of taste processing is not yet clear and needs further investigation. Results

from my study may support the notion that this shift is related more to the central components of taste, such as the hedonic area in the brain, as well as the learning process, as a result of the post-ingestive effects of certain foods following VSG, a response that we may call “conditioned aversion”. A similar pattern was seen as that of high-fat diet-induced obese rats, which “like” high concentrations of sucrose and corn oil. Rats post RYGB shift “liking” from higher to lower concentrations of both sucrose and corn oil solutions, behaving similarly to lean rats using the taste reactivity test (384). And because restricted-calorie diet-induced rats experienced the same shift, the mechanism appeared to depend on weight loss rather than some other effect of the surgery (384). In the literature on humans, liking has been measured questionnaires and the VAS (612). Like the findings in rats, RYGB patients preferentially reduced their liking of high-calorie food versus low-calorie foods, as measured before and after surgery (613).

Patients with obesity described higher hedonic hunger (361) and higher liking for a given sweetness (471), compared with normal weight patients. Remarkably, this occurs regardless of decreased perceived sweetness in patients with obesity (471). Consequently, as determined by Bartoshuk et al. (471), liking is increased as a function of sweetness in patients and more as BMI increases, and for similar perceived sweetness, liking increases as BMI increases. Interestingly, my results have also shown a correlation between weight reduction and the ingestive effect, the more weight reduces the less the ingestive effect is. During the early postsurgical phase, as a large amount of weight loss occurs, aversive conditioning might play an important role in the reduction of food intake in both humans (614) and rats (383). During the later postsurgical phases, changes in circulating gut hormones acting on the brain are supposed to be the main candidates for reduced appetite and food intake (292).

7.1.6 Strength: Methodology

One of the fundamental components of the task used is that the assessment is based on the actual behaviour of the adolescent subject and is not loaded by some of the informative limitations associated with scaling procedures. The strength of this study is that actual direct measures of portion size, meal duration and eating rate were possible, both preoperatively and up to 1 year postoperatively. Direct assessments of portion sizes are certainly preferable, even if it is possible to rationally estimate the meal size based on assumed energy requirements. Even more exciting is the meal duration and eating rate, which add new and potentially significant clinical knowledge that are both important for clinicians in the nutrition care process and for the patient in daily life. Our study also answered the question of how hard was an adolescent subject willing to work for a given reinforcer. Consummatory behaviour in adolescents, as compared to the pre-surgical phase, was determined using direct measure changes in “facial expressions” in adolescents when reacting to tastant stimulants after VSG. Our study proved that facial expressions might be suitable to measure dislike, as well as suitable to measure various gradients of food acceptance in adolescent obese patients. In contrast to earlier experiments, the method of constant stimuli was used, in which taste stimuli were presented randomly and performance was assessed across a set of concentrations, allowing for derivation of a psychometric function. Furthermore, adolescent subjects obtained feedback by receiving tokens for correct responses and losing tokens for incorrect responses, which seemed to keep subjects attentive and motivated in this game-like competitive setting.

7.1.7 Limitation: Eating behaviour and meal pattern

A limitation of this study is that the test meals were administered in a laboratory setting, which may not reflect habitual eating habits of patients. In human research, food choice is regularly assessed by having patients maintain a food diary for a period of time, then analysing their diet by categorising

foods in different ways. Whereas total calorie intake and macronutrient intake can be calculated in a straightforward method, there is no consensus for grouping foods into other categories. For example, ice cream is differentially classified in four different studies as “dessert”, “sweets”, “milk and ice cream”, and “energy dense” (332; 362; 363; 368). In human research, there is a major need for the acceptance of a standardised classification of foods. This may help to stop categorisation and analysis according to the investigator’s interests, and would facilitate comparisons between studies. The limitations of the study include the relatively small sample size, for both VSG and control group of adolescents that may possibly affect the generalisability of the results. It was not easy to bring subjects of this age group for testing in the morning, missing classes at school, and this was the main limitation to getting the control group to attend for a 3rd visit, unlike the VSG subjects. This difficulty was despite attempting to match test visits with children’s surgical check-up appointment at the obesity clinic. Also, the current study lacks data on changes in physical activity and body composition after VSG surgery for this age group. This information may have increased our understanding of associations or a lack thereof, between changes in food weight, energy intake, energy density and weight loss after VSG surgery. In addition, it has not been possible to measure the effect of the pediatric obesity clinic routine preoperative dietary education for adolescents with obesity, which may have had diverse effects in different subjects on postoperative eating behaviour. One of the limitations of using visual analogue scales in single-meal studies is that they have a great inter-individual variability. Nevertheless, this may be of less concern in this within-subject design.

7.1.8 Limitation: Taste detection

A limitation of this study was the age group (12-18 years). An age group including subjects of less than 15 years old is not recommended for this study design, because of the methods setting, including the duration, need to focus, engagement and fasting hours. Age group of (15-18) years is preferable and much easier for the investigator to deal with for such behavioural studies. Children’s

attention deficiency test screening is required for further studies of similar methodology for this age group.

7.1.9 Limitation: Appetitive behaviour

It's not possible to entirely dismiss the possibility that subjects' responses were influenced by their own cognitive expectations regarding how they thought they were supposed to behave toward the reward stimuli. However, this is an inescapable limitation of any assessment of food preference and hedonics in an experimental setting. Teeth screening wasn't included in the inclusion/exclusion criteria, which might affect the intake of the sweet/fatty candy.

7.1.10 Limitation: Consummatory behaviour

Limitations may include the participant's own interpretation of their sensation and are thus subject to variation based on individual differences in prior sensory experience. The adolescent subjects maybe holding back their responses as they feel that there were video recordings and this may lead to false reporting. The major limitation to the use of facial reactivity is the difficulty in interpretation of these often small and subtle movements (535). A few studies have used the Facial Action Coding System (FACS) with trained interpreters (540). However, new face recognition software packages have recently been developed, which enable the more objective assessment of facial reactivity and the duration of the facial reaction, providing better overall feedback on the emotional state of the subject (e.g. FaceReader™). This technology is promising and could be further improved in terms of specificity, sensitivity and adapted to cultural and social facial reactivity differences. Another limitation of this study is its small sample size, both for VSG and control groups, which limits the generalisability of the results.

7.1.11 Limitation: Methodology

A limitation of this study is that the test meals were administered in a laboratory setting, which may not reflect habitual eating habits of patients. Scaling procedures have their limitations, but are relatively easy, efficient and inexpensive to use. This is also applied to all dietary verbal questionnaires that depend on memory, reliability, and good skilled interviewer. Another limitation of the study was the age group (12-18), an age group less than 15 years old are not really recommended for some of the study objectives, because of the methods' setting itself. Age group of (15-18) years are preferable and easier to deal with for such behavioural studies.

7.1.12 Findings Potential Interaction Discussion

In addition to potential changes in the sensory nature or unconditioned hedonic value of sweets, there are other explanations for avoidance of some sugary or fatty foods and fluids after surgery. These include learning from post-ingestive consequences and nutritional counselling (269;271;275;368;518;586;587). Understanding behaviours, such as ingestive behaviour, is an essential developmental mechanism critically guided by the brain reward system. When defining the relationship between food reward and obesity it is not yet clear what comes first. Several human and rodent studies that state changes in food choices and preferences were recently reviewed (364;615;616). The common observation in human studies of a shift from sweet and fatty energy-dense foods to less energy-dense foods (367), is comparable to rodent studies, which find a shift in preference from high-fat diets before surgery in the obese state, to a lower preference for such diets after both RYGB and VSG (303;383;464;529;617). The diminution of fat preference in response to intra-gastric infusions of sucrose and intra-lipid, following bariatric surgery, suggest that the effect of VSG surgery on meal size might result from increases in sensitivity toward the caloric content of a given food, rather than resulting in increased distension-related signals due to small stomach (577).

Thus, this could be a good correlate for meal termination (618). However, preference and reward pathways are possible products of a more complex pathway that contains higher forebrain circuits. The different postprandial hormone profiles post VSG might be related more to changes in nutrient delivery to the duodenum. Human data demonstrate that VSG significantly increases the gastric emptying rate (461;462;619) and transit (462), and, in RYGB subjects, transit is increased by the surgical construction of a gastric-jejunal anastomosis (620). A previous study showed that rats increased their carbohydrate intake relative to fat through food selection test (462;529), suggesting that patients who undergo VSG will also be less likely to select high fat foods. However, it has been shown that, even when rats are continued on a similarly high-fat diet to that used to make them obese before the surgery, VSG still results in great reductions in body fat. Such results may suggest that changes in food choice are not essential to reduce body weight after VSG. Nevertheless, it is possible that similar mechanisms that lead to body weight reduction, also act to alter food choice as well (577).

Accelerating the transit of lipids into the distal gut could stimulate the release of supra-physiological levels of GLP-1, PYY, and insulin after these types of surgery (301;314;462;621;622). It could also limit the exposure of fat to lipases and the emulsification process, providing a potential reason for the observed increase in plasma bile acids after VSG (623) and RYGB (624), as well as reduction in fat preference. This hypothesis might explain the differences between VSG and restrictive procedures such as AGB, wherein gastric emptying rates are not increased (625;626), and postprandial hormone profiles are not changed (290;316). In previous studies it was shown that the effects of RYGB on food preferences have been attributed to the exclusion of the duodenum and proximal bowel. However, the profile produced by VSG rats, on dietary preferences for high-energy liquids and dietary fat, reveals that similar effects can be achieved without bypassing the intestine. It also shows that reduction of meal size after VSG is due to an activation of satiation pathways in response to

nutrients, and especially to fat content, rather than as a result of volume effects (577). These data support the hypothesis that the satiating effects of VSG are based upon changed perceptions and actions of calories, not altered perception of the volume, caused by mechanical restriction as suggested previously (577).

The noticeable changes in ingestive behaviour, with smaller meals and shifts in preference, observed in humans and rodents after RYGB (244;263;367;384;616;627) suggest that learning mechanisms contribute, in order to avoid unpleasant gastrointestinal sensations such as fullness, nausea and pain when ingesting too much of certain foods. Bariatric surgery in humans often causes incidences of fullness, discomfort and nausea, sometimes even pain and vomiting, with differing intensity and frequency, depending on the type of bariatric procedures (628-632) and the occurrence of a complication. Furthermore, conditioned taste aversion to orally administered corn oil was demonstrated in rats after RYGB and VSG (383;529). Changes in attitudes to eating may also alter meal frequency, meal size, eating rate (547;573), and weight loss maintenance (574-576). Individuals may be influenced by psychosocial factors, such as, culture, dietary counselling, food preferences, previous experiences of dieting and emotional state (244). The changes in gastrointestinal physiology after VSG may begin with a cognitive process where the individual makes changes in their behaviour, or may try to avoid negative consequences of eating specific foods (633). This learning process may increase cognitive restraint, although the impact this may have is controversial (546).

When bariatric surgery patients are asked to describe their eating experience using interpretative phenomenological analysis, self-control was the central theme permeating all areas of the interviews (634;635). Most of these patients have been struggling all their life with control over eating and successful surgery appeared to make control easier. Ogden et al. concluded that successful surgery without weight regain brings the patient's mind 'in gear', while failed surgery is characterised by a continuing battle for control (635). While the liking and wanting systems generate incentive

salience and craving, the executive control system acts as a brake to align impulsive behaviour with longer-term goals. Inhibitory control is particularly important to resist allurements to eat as stimulated by pervasive food cues in the modern environment (610). It would appear then, that the success of bariatric surgery may be due, in part, to the post-operative ability of an individual to activate neural circuits involved in executive control (636). It is unclear whether executive functions are precisely impaired in obesity or preoperatively in RYGB patients and VSG. The level to which the hedonic value of a given food cue impacts executive control functions also remains to be determined. RYGB post-operative changes in food hedonics may also facilitate executive control functions (613), and this is maybe the case in VSG. If this is the case, then removing or reducing the hedonic value of notoriously high-calorie foods through RYGB and VSG would make it easier to self-regulate their intake (610).

Food preferences and choices are direct reflections of sensory hedonic responsiveness, a justification for research on orosensory acuity, “wanting” and “liking”. In spite of the limited and inconsistent evidence this may explain the variation in energy intakes or nutritional status. Additionally, an aim of numerous public health (and marketing) campaigns is to attempt to shift a consumer choice toward certain foods. This fact alone places the understanding and ability to guide food “likes” and “wants” as a dominant challenge to academic and industrial nutritionists and consumer research. As noted earlier, attention to the differences between “liking” and “wanting” was considered (637).

Considerable attention has also been given to the insight of orosensory stimuli and explicit liking of foods; however variation in obesity is not yet evidently related to variation in the hedonic knowledge or pleasure of eating. This apparent inconsistency may be resolved by a growing body of behavioural and neurophysiological evidence that distinguishes “liking” and “wanting”, and suggests new insights for understanding (over-) eating and obesity and the mechanisms behind.

Does this have any real-world application? It's worth understanding "why we want to eat what we want to eat". It's important to know that at any given moment a conscious feeling of the desire to eat a specific food is the result of a balance of: (1) physiological state and signals (particularly, thirst and hunger); (2) anticipated pleasure of eating (mainly acquired from learned associations); and (3) external associations and signals (also mainly learned, with cognitive components as well as elements that may be unrecognized and unconscious)(637).

Implications

What are the implications of all this? And how can we benefit from this in public health?

For investigation in food intake and appetite regulation, by putting emphasis on understanding the nature of externally signalled eating behaviour, and particularly the extent and reason of differences in sensitivity to this (together with cognitive restraint and dieting) and its mechanism.

For investigation in sensory food science and food acceptance, this body of knowledge must be integrated with consideration of the dynamics of the acquisition and changes in "liking", and "wanting".

For guidance in prevention and treatment of obesity, this may give description to methods emphasising environmental control, with structuring and limiting food stimulation.

For commercial food developers, the challenge in relative to weight control remains to improve the quality and attractiveness of lower dense foods, and make sure they are not just "liked", but also "wanted".

For commercial food marketers, understanding this area of research, might point on the role of environmental signals, which include food itself as stimulus to eat. Marketers must take

responsibility to guarantee that they are not excessively adding to the environmental stimulation to eat inappropriately.

The main challenge is to understand the taste mechanism, the orosensory acuity, “wanting” and “liking”, the drivers of variance in eating behavior and food preferences and choices, and to apply this knowledge to food development, marketing, and public health guidance in ways that make healthy, appropriate eating somewhat that is liked, wanted, and preferred, as a preventive measures and management tools for childhood and adult obesity.

CHAPTER 8

SUMMARY

8.1 Summary

In summary, food preferences reported by adolescent patients undergoing VSG suggest a shift in food preferences to healthier choices, a reduction in fat and high glycaemic index carbohydrates with an increase in low glycaemic index carbohydrates and unchanged protein intake after VSG. Patients reduced their *ad libitum* meal size, meal duration and eating rate. Habitual meal frequency tended to increase, with more meals consumed in the mornings. Emotional and unconditional eating decreased, while cognitive restraint increased after VSG. Besides a considerable reduction in overall energy intake, patients also reported decreased dietary energy density. Thus obese adolescents after VSG exhibit eating behaviour that might help in promoting and maintaining weight loss.

Obesity is associated with complex alterations in food reward functions at the neural and behavioural level. Generally, obese subjects like and want palatable foods more than normal weight subjects. Thus, there is clear evidence that ingestive behaviour and food choice changes after bariatric surgeries (RYGB and VSG) and that eating 'as usual' can lead to discomfort and nausea. It is thus very reasonable that animals and humans learn to avoid these negative consequences and thus reduce food intake, a term that we call the "conditioned aversion" response. It may, therefore, be possible to take advantage of this system for the development of drug or behavioural therapies to restrain food intake without induction of nausea (610).

CHAPTER 9

CONCLUSION AND FUTURE DIRECTIONS

9.1 Conclusion

Adolescent patients after VSG showed a shift in food preferences to healthier choices, with considerable reduction in overall energy intake and decreased dietary energy density. Eating behaviour and meal pattern changed, patients reduced their ad libitum meal size, meal duration and eating rate, as well as changes in the attitude of eating. All together this might help in promoting and maintaining weight loss. Obesity is associated with complex alterations in food reward functions at the neural and behavioural level. VSG was able to determine changes in the hedonic value, the reward domain in the brain, by changing the appetitive and consummatory behaviour in response to sweet or fatty stimulants, and shows no effect on the sensory domain, sweet sensitivity, after surgery.

9.2 Future work

Throughout the past decade, there has been a flow in studies characterising the effects of bariatric surgery in humans and rodents. They have established many structural, functional and molecular changes in the gut, the brain and the other organs as well as alterations in energy metabolism, glucose homeostasis and behaviour. After going for the 'low-hanging fruit', it is now time to separate irrelevant changes from mechanistically relevant ones. The marked and constant body weight loss and attendant correction of much obesity-related impairment in metabolism and behaviour are well-documented, while other effects that do not depend on the hypocaloric state and weight loss are variable and less clear.

In general, while the constant body weight loss in humans is mainly elucidated by reduced energy intake, not increased energy expenditure, the key observation is that energy intake is not increased to regain lost body weight, though food intake can be doubled if properly stimulated. This proposes

the active defense of a new lower body weight level post-surgery. Therefore, explaining the potential mechanisms for this constant relative hypophagia is perhaps most crucial for future non-surgical treatments of obesity. Whereas a number of candidate mechanisms have been proposed on the basis of changes in gut hormone secretion, as well as changes in peripheral and central targets of such hormones, direct testing of individual signaling flows was unable to confirm any of these hypotheses so far. It was beyond the scope of this study to explore the mediators of the change in appetitive and consummatory behaviour after VSG. It is notable that responses of post-prandial anorexigenic gut hormones (glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY)) are enhanced after both the VSG and RYGB, in spite of the anatomical differences between both procedures. The administration of GLP-1 and PYY has been shown, not only to increase fullness and decrease caloric intake, but also to decrease behavioural and brain reward system responses to energy-dense food or cues in humans and rodents. Reports of changes in taste-guided behaviour and food choices after bariatric surgery in the literature are mixed. Studies including more direct measures of target behaviours may help explain whether changes in food selection and changes in taste function accompany the reduction in caloric intake and weight loss seen after bariatric surgery. This goal can possibly be achieved through the implementation of protocols similar to those used with animals in basic research. The application of these techniques may also facilitate translation between findings from rodent models, which are essential for explaining physiological and neural mechanisms, and clinical research regarding the effects of VSG on taste function and food selection in humans.

The priority for future research that is aimed to:

1-Studying the changes in dietary energy density after VSG and RYGB using direct measure methodology. A standardised *ad libitum* meal (lunch), in a buffet style, will be served to all participants, who will be free to choose and consume as much as they wish.

The energy intake (EI) and the dietary energy density (DED) of the food choice will be calculated after weighing the served food before and after the test meal. Meal patterns will also be measured using a standardised questionnaire for the analysis of meal frequency, dietary behaviour and temporal distribution over 24 hours, because the work showed changes in meal pattern and eating behaviour post VSG

2- Studying the consummatory behavior of taste in adolescent humans after it has showed some promising results using facial reactivity methods. The aim is to study the taste reactivity on a larger scale of subjects using the facial analysis software programs method such as the FaceReader® for more objective results.

CHAPTER 10

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CHAPTER 11

APPENDICES

Appendix 1 Review of studies from Saudi Arabia evaluating the prevalence of overweight and obesity among children (Adapted following permission from the author; Al-Dossary S.S.)

Review of studies from Saudi Arabia evaluating the prevalence of overweight and obesity among children							
Reference	Region	Target children	No.	Ages (years)	Sex	Overweight prevalence (%)	Obesity prevalence (%)
Present study	Eastern province	School children, Private hospital	7056	2-18	M, F	19	23.3
Alarm, 2008	West Riyadh	Elementary school	1072	8-12	F	n/d	14.9
Amin, 2008	Al Hassa	Primary schools	1139	10-14	M	14.2	9.7
Al-Hazzaa, 2007	Riyadh	Primary schools	1082 (1988) 702 (2005)	6-14	M		3.4 (1988) 24.5 (2005)
Al Turki, 2007	Riyadh	Primary care clinic	267	12-20	n/d	18.7	21.0
Mahfouz, 2007	Abha city	Schools	2696	11-19	M	11	5.0
Farghal, 2007	Abha city	Schools	767	7-20	M, F	11	15.9
Al-Almaie, 2005	Al-Khobar	Intermediate and all 3 grades of secondary school	1766	14-19	M, F	19.3(M) 11.8(F)	17.2(M) 10.2(F)
Al-Rukban, 2003	Riyadh	Intermediate and secondary schools	894	12-20	M	13.8	20.5
Al-Saeed, 2003	Different provinces	Primary and preparatory schools	2239	6-17	F	20	11.0
El-Hamzi & Warsy, 2002	Different provinces	Household screening programme	12701	1-18	M, F	23.4	12.7
El-Hamzi, 2002	Different provinces	National epidemiological household	12071	1-18	M, F	10.7(M) 12.7(F)	6.0(M) 6.7(F)

Abahussain, 1999	Al-Khobar city	Adolescent girls	676	12-19	F	28 (overweight obese)	
Al-Nuaim, 1996	Different provinces	Schoolchildren	9061	6-18	M	11.7	15.8

M = Male; F= Female
n/d = not determined

Appendix 2 Non-Surgical treatment for obesity: type of weight-loss interventions, diets, meal replacements, exercise, and weight loss medications with different outcomes. Studies age group for both males and females was between 22-65 years old.

Baseline data, number of study completers, study duration, type of weight-loss interventions that contribute to successful outcomes									
Study	No. enrolled	No. of completers	Mean baseline BMI ^a	Total study duration (wks)	Treatment duration (wks)	Mean weight Loss (kg)			Interventions ^b
Diet alone ^c			Mean $\pm$ standard deviation			6 m	12 m	Final	
Bacon and colleagues, 2002	78	54	35.7 $\pm$ 3.6	52	26	4.6	5.9		
						0.5	1.3		DA
Brink worth and colleagues, 2004	58	43	34.1 $\pm$ 1.8	68	12	8.7	3.7	2.7	AA
						7.2	3.2	3.8	DA
Burke and colleagues, 2002	63	63	30.6 $\pm$ 2.9	64	17	5.5	5.1	6.6	DA (high-protein diets)
						1.9	1.9	0.3	DA
Djuric and colleagues, 2002	48	39	35.5 $\pm$ 3.9	52	NA ^d	7.9	8		AA
						9.3	9.4		DA
						3	2.6		DA + Weight Watchers (WW)
						1	0.9		AA (referred to WW)
Foster and colleagues, 2003	63	37	34.3 $\pm$ 3.8	52	NA	9.6	7.2		AA
						5.2	4.4		DA (low CHO * high protein diet)

Heshka and colleagues, 2003	423	309	33.7±3.7	104	NA	5.8 1.8	5 1.4	3 0.1	AA DA (WW)
Jones and colleagues, 1999	112	102	34±6	150	12	3.2 1.8	1.7 1.4	1.2 2.2	AA DA
Manning and colleagues, 1998	205	145	32 (29.8-34.3) ^f	208	26	2.7 NA	2.3 1.2	1.7 NA	AA DA
McManus and colleagues, 2001	101	61	33±5	78	26	5.1 4.9	5 4.8	2.9 4.8	AA DA
Pritchard and colleagues, 1998	270	177	NA	52	52	NA NA	6.2 0.7		DA (moderate fat: 35%) DA
Ramirez and colleagues, 2001	88	65	33.8±5.1	52	16	NA NA	6.6 5.6		AA DA
Rapoport and colleagues, 2000	75	63	35.4 6.3	52	10	3.5 2	3.6 1.9		DA + body image therapy DA
Sbroco and colleagues, 1999	24	21	32.6±3.6	52	15	4.5 7	4.3 10.1		AA DA
Stern and colleagues, 2004	132	126	42.9±7.7	52	4	1.9 5.8	3.1 5.1		DA + cognitive behavioral program DA
Toubro and colleagues, 1997	43	37	36.5 (33.8-37.7) ^f	121	17	13.1 15.8	9.7 15.5	2.5 8	DA (low CHO diet) DA (follow-up: fixed energy intake)

Trials of Hypertension 1997	2.382	2.202	NA	156	26	4.3	NA	0.3	DA (follow-up: ad lib, low fat, high CHO diet)
						0.6	NA	1.8	DA
Turnin and colleagues, 2001	557	341	33.3±0.5 [§]	52	NA	NA	NA	NA	AA
						NA	NA	NA	DA
Whelton and colleagues, 1998	585	532	31.2±2.5	150	35	5	4.7	4.7	DA + follow-up, Internet program
						1.1	1.1	0.9	DA
Wolf and colleagues, 2004	147	117	37.6±7.7	52	52	3.8	2.4		AA
						0.7	0.6		DA
Womble and colleagues, 2004	47	31	33.4±3.2	52	NA	1.2	2		AA
						3.5	3.9		DA (eDiets.com)
Wylie-Rosett and colleagues, 2001	588	476	35.6±6.5	52	NA	NA	3.4		AA
						NA	2.1		DA
						NA	3.4		AA + computer kiosks
Exercise alone	No. enrolled	No. of completers	Mean baseline BMI ^a	Total study duration (wks)	Treatment duration (wks)	Mean weight Loss (kg)			Interventions ^b
			Mean ± standard deviation			6 m	12 m	Final	
Donnelly and colleagues, 2000	22	22	31.2±5.1	78	78	NA	0.5	1.7	EA (continuous exercise)
						NA	1.9	0.8	
Donnelly and colleagues, 2003	131	74	29.2±3.2	78	78	2.6	1.9	2.3	EA (intermittent exercise)
						0.4	0.9	1.2	EA

Irwin and colleagues, 2003	173	168	30.5±(29.6-31.4) ^f	52	52	NA	1.3		AA
						NA	0.1		EA
Pritchards and colleagues, 1997	68	58	28.9±2.8	52	NA	NA	2.6		AA
						NA	0.9		EA
						NA	6.4		AA
Diet and exercise	No. enrolled	No. of completers	Mean baseline BMI ^a	Total study duration (wks)	Treatment duration (wks)	Mean weight Loss (kg)			Interventions ^b
			Mean ± standard deviation			6 m	12 m	Final	
Anderson and colleagues, 1999	40	33	31.9±4.5	68	16	8.3	NA	6.7	DE (structured aerobic exercise)
						7.9	NA	7.8	
Ashutosh and colleagues, 1997	37	31	NA	52	25	NA	15.8		DE (moderate lifestyle activity)
						NA	14.5		DE
DPP 2002	3,234	2,991	34.0±6.7	208	24	7	7	4	DA
						0.1	0.1	0.1	DE
Esposito and colleagues, 2003	120	112	34.9±2.4	104	52	NA	NA	14	AA
						NA	NA	3	DE
Fleming and colleagues, 2002	120	100	NA	52	NA	NA	17.2		AA
						NA	2.7		DE
Harvey-Berino and colleagues, 2002	122	90	32.4±4.8	78	24	9.8	9.8	10.4	AA
						8	6	5.7	DE (in-persons support)
						11	10.6	10.4	DE (Internet support)

Harvey-Berino and colleagues, 2004	255	176	31.8±4.1	78	26	7.6	7.5	5.1	DE (minimal in-person support)
						8.4	10.1	7.6	DE (in-person support)
						7.6	7.1	5.5	DE (Internet support)
Jakicic and colleagues, 1999	148	115	32.8±4.3	78	26	10.2	8	7.6	DE (minimal in-person support)
						9.3	6	5.2	DE (long bout exercise)
						10.2	11	8.4	DE (short bout exercise)
Jakicic and colleagues, 2003	201	184	32.6±4.2	52	26	9.4	8.8		DE (short bout and exercise equipment)
						8	8.2		DE (vigorous intensity/high duration exercise)
						7.1	6.4		DE (moderate intensity/high duration exercise)
						7.5	6.9		DE (moderate intensity/moderate intensity exercise)

Jeffery and colleagues, 2003	202	168	31.1±2.5	78	26	9	8.5	6.7	DE (vigorous intensity/moderate duration exercise)
						8.1	6.1	4.1	DE (2,500 kcal/wk exercise)
Leemakers and colleagues, 1999	67	57	30.8±4.5	78	26	9.6	7.9	6.9	DE (1,000 kcal/wk exercise)
						8.7	8.5	8.1	DE (weight maintenance exercise-focused)
Perri and colleagues, 1997	49	40	33.6±4.5	65	26	10.9	10.1	9.2	DE (weight maintenance weight-focused)
						10.6	12.4	11.9	DE (moderate exercise in groups)
Racette and colleagues, 2001	69	36	40±2	52	1	5.3	4.6		DE (moderate exercise at home)
						NA	0.3		DE
Rejeski and colleagues, 2002	278	222	34.5±5.8	78	26	NA	NA	4	AA
						NA	NA	5.4	DE
						NA	NA	1.2	DA
						NA	NA	2.4	AA
Tuomilehto and colleagues, 2001; Lindstrom and colleagues, 2003	522	471	31.2±4.6	156	52	NA	4.2	3.5	EA
						NA	1	0.9	DE

Wing and colleagues, 1998	154	129	36.0±5.4	104	52	10.3	7.4	2.5	AA
						9.1	5.5	2.1	DE
						1.5	0.3	0.3	DA
						2.1	0.1	1	AA
Wing and colleagues, 1999	166	136	31.2±4.0	60	52	5.3	NA	3	EA
						6.1	NA	3	DE
						8.8	NA	4.7	DE + social support
						8.7	NA	4.7	DE+3 friends
Very-low-energy diet	No. enrolled	No. of completers	Mean baseline BMI ^a	Total study duration (wks)	Treatment duration (wks)	Mean weight Loss (kg)			Interventions ^b
			Mean ± standard deviation			6 m	12 m	Final	
Borg and colleagues, 2002 Fogelholm and colleagues, 2003	90	68	32.9±2.6	134	8	13	12.1	5.3	
						14	12.3	4	2 mo VLED followed by DA
						15.5	14.9	6.1	2 mo VLED followed by wt maintenance walking group

	85	80	34.0 (29-46) [†]	52	12	13.5	1.7	2 mo VLED followed by wt maintenance resistance training group	
						12.6	0.5	12 wk VLED followed by DA	
Lantz and colleagues, 2003	334	117	40.0±5.7	104	16	20.6	15	7	12 wk VLED followed by weight maintenance walking group
Paisey and colleagues, 2002	45	25	36.8±9.9	260	6	22	17	9.1	16 wk VLED with VLED 2 wks every 3 mo
						14.5	13.5	8.9	16 wk VLED with VLED on-demand with wt regain
						3	2	1	6 wk VLED followed by DA
Pasman and colleagues, 1997	44	31	33.2±3.7	69		9.8	5.3	1.4	DA
Rössner and colleagues, 1997						11	8.3	4.4	6 wks VLED followed by DA with fiber supplement

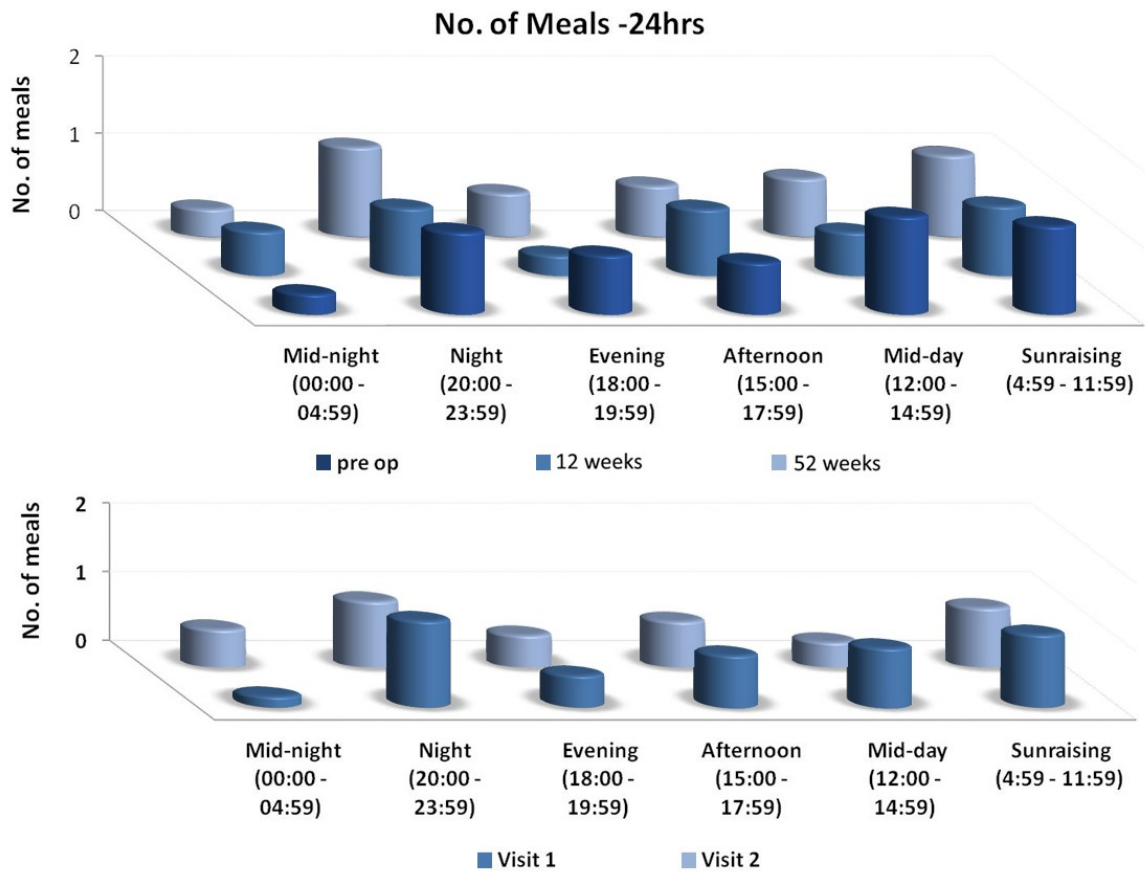
	98	93	38.7±5.2	52	6	20.1	15.1	6 wks VLED followed by DA without fiber
						18.3	12.1	6 wks VLED followed by DA
Ryttig and colleagues, 1997	81	42	37.7±5.7	104	8	18.2	12.3	5.8 6 wks 880 kcal/d followed by DA
						10.2	5.5	5.5 2 mo VLED followed by DA
Stenius-Aarniala and colleagues, 2000	38	38	30-42 ^l	52	8	14.2	11.1	DA
						0.3	2.3	8 wk VLED followed by DA
Torgerson and colleagues, 1997	113	87	40.4±4.3	104	12	17	14	9.2 AA
						7	7	6.3 12 wks VLED followed by DA
Torgerson and colleagues, 1999	121	73	38.0±5.0	52	16	19.1	12.3	DA
						14	10.2	16 wk VLED followed by DA
						13.2	8.6	16 wk VLED in metabolic ward followed by DA

Van Aggel-Leijssen and colleagues, 2002	37	22	32.1±2.6	52	12	14.8	8.9	16 wk VLED plus 2 meals/wk followed by DA	
						15.4	7.1	12 wk VLED followed by DE	
Orlistat and diet	No. enrolled	No. of completers	Mean baseline BMI ^a	Total study duration (wks)	Treatment duration (wks)	Mean weight Loss (kg)			Interventions ^b
			Mean ± standard deviation			6 m	12 m	Final	
Bakris and colleagues, 2002	532	270	35.6±4.0	52	NA	5.5	5.4		O
						2.8	2.7		
Broom and colleagues, 2002	522	327	37.0±6.4	54	54	6	5.8		DA
						2	2.3		O
Davidson and colleagues, 1999	880	403	36.3±0.9	104	52	7.8	8.8	5.6	DA
						6.2	5.8	2.1	O
Finer and colleagues, 2000	228	139	36.8±3.7	52	NA	9	8.8		DA
						6.7	5.4		O
Hanefeld and colleagues, 2002	383	264	34.0±5.6	52	NA	4.5	5.3		DA
						3.5	3.4		O
Hauptman and colleagues, 2000	635	328	36.0±0.3 [§]	104	52	8.5	8.4	4.9	DA
						5.5	4.3	1.5	O
Hill and colleagues, 1999	1313	537	32.8±0.2 [§]	76	24	10	NA	6.2	DA
						10	NA	5.9	O

Hollander and colleagues, 1998	322	254	34.3±3.4	52	NA	5	6.3		DA
						3.7	4.2		O
Kelley and colleagues, 2002	535	265	35.7±0.3 [§]	52	NA	4.3	3.9		DA
						1.8	1.3		O
Krempf and colleagues, 2003	696	425	36.1±0.3 [§]	78	NA	7	7.3	6.4	DA
						4	4.4	2.7	O
Miles and colleagues, 2002	516	311	35.4±0.3 [§]	52	NA	5	4.7		DA
						2.1	1.8		O
Sjöström and colleagues, 1998	743	435	36.1 (28.3-47.2) [†]	104	52	10	10.3	8	DA
						8	6.1	5	O
Torgerson and colleagues, 2004	3305	1414	37.4±4.5	308	26	10.1	10.6	5.8	DA
						6.4	6.2	3	O
Meal replacement	No. enrolled	No. of completers	Mean baseline BMI ^a	Total study duration (wks)	Treatment duration (wks)	Mean weight Loss (kg)			Interventions ^b
			Mean ± standard deviation			6 m	12 m	Final	
Ditschuneit and colleagues, 1999	100	75	33.3 4.1	108	12	9.1	9.1	9.5	
						3.5	3.7	4.1	MR
Rothacker and colleagues, 2001	75	64	28.9 1.7	52	12	6.3	6.4		DA
						3.8	1.2		MR
Hensrud, 2001	33	24	31.0 4.2	52	12	4.7	1.3		DA
						3	1		MR
Ashley and colleagues, 2001	74	74	30.0 3.1	52	NA	5.8	5.6		DA
						2.3	3.4		MR

Ahrens and colleagues, 2000	95	51	31.0 4.2	52	NA	4.9 4.4	8.2 9.5	DA MR	
Metz and colleagues, 2000	302	250	33.1 4.9	52	NA	7.8 2.4	5.8 1.7	DA MR	
Wadden and colleagues, 2004	123	82	35.9 4.5	65	40	12.2 7.8 0.1	9.6 7.5 0.1	8.3 6.2 0.1	DA MR DA
aBMI=body mass index. bDA=diet alone; AA=advice alone; DE=diet and exercise; EA=exercise alone; MR=meal replacement; VLED=very-low-energy diet; O=orlistat; S=sibutramine. cStudies have diet alone (reduced energy intake, basic behavioral strategies, and general advice for exercise) as the primary weight-loss intervention. dNA=not available. eCHO=carbohydrate. fMeans±95% confidence intervals. gMeans ±standard error of the mean.					hStudies have diet and exercise (reduced energy intake, basic behavioral strategies, and specific goals for exercise) as the primary weight-loss intervention. iStudies have exercise alone (specific guidelines for exercise, no specific recommendations for diet) as the primary weight-loss intervention. jStudies have meal replacements as the primary weight-loss intervention. kStudies have a very-low-energy diet as the primary weight-loss intervention. lRange. mStudies use orlistat and diet as the primary weight-loss intervention.				

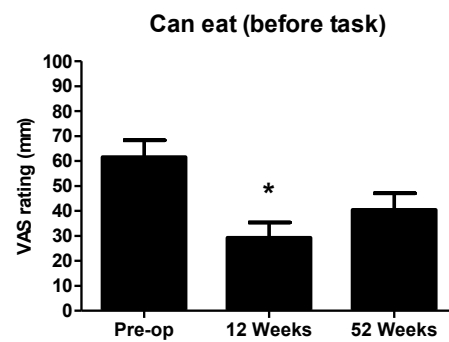
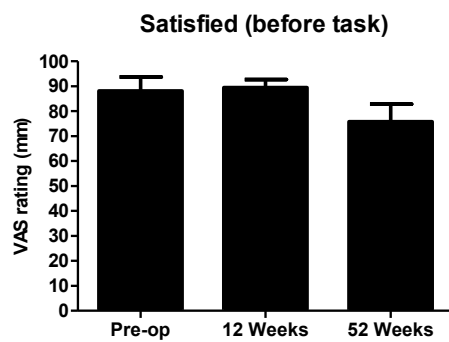
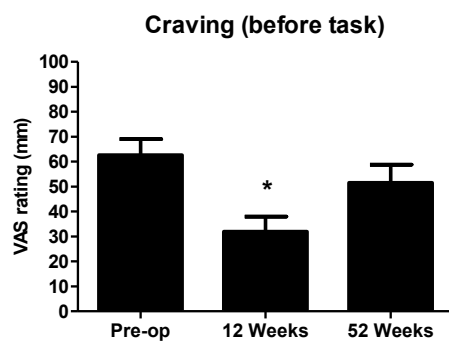
Appendix 3 Meals distribution over the 24 hours (Chapter 3)

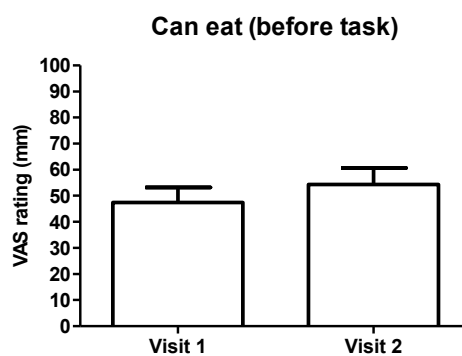
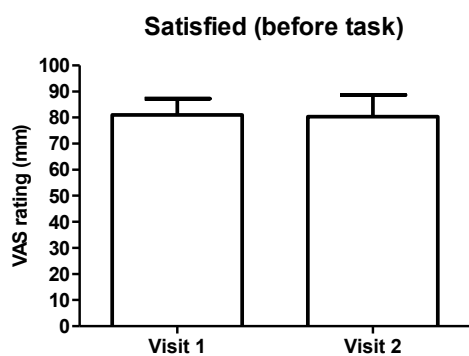
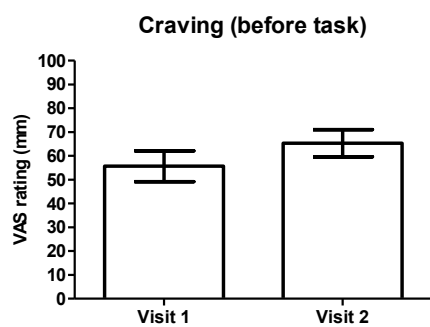


Number of meals distributed over the 24 hours for VSG and control subjects

Appendix 4 Visual Analogue Scale Ratings for VSG and control subjects throughout interval visits

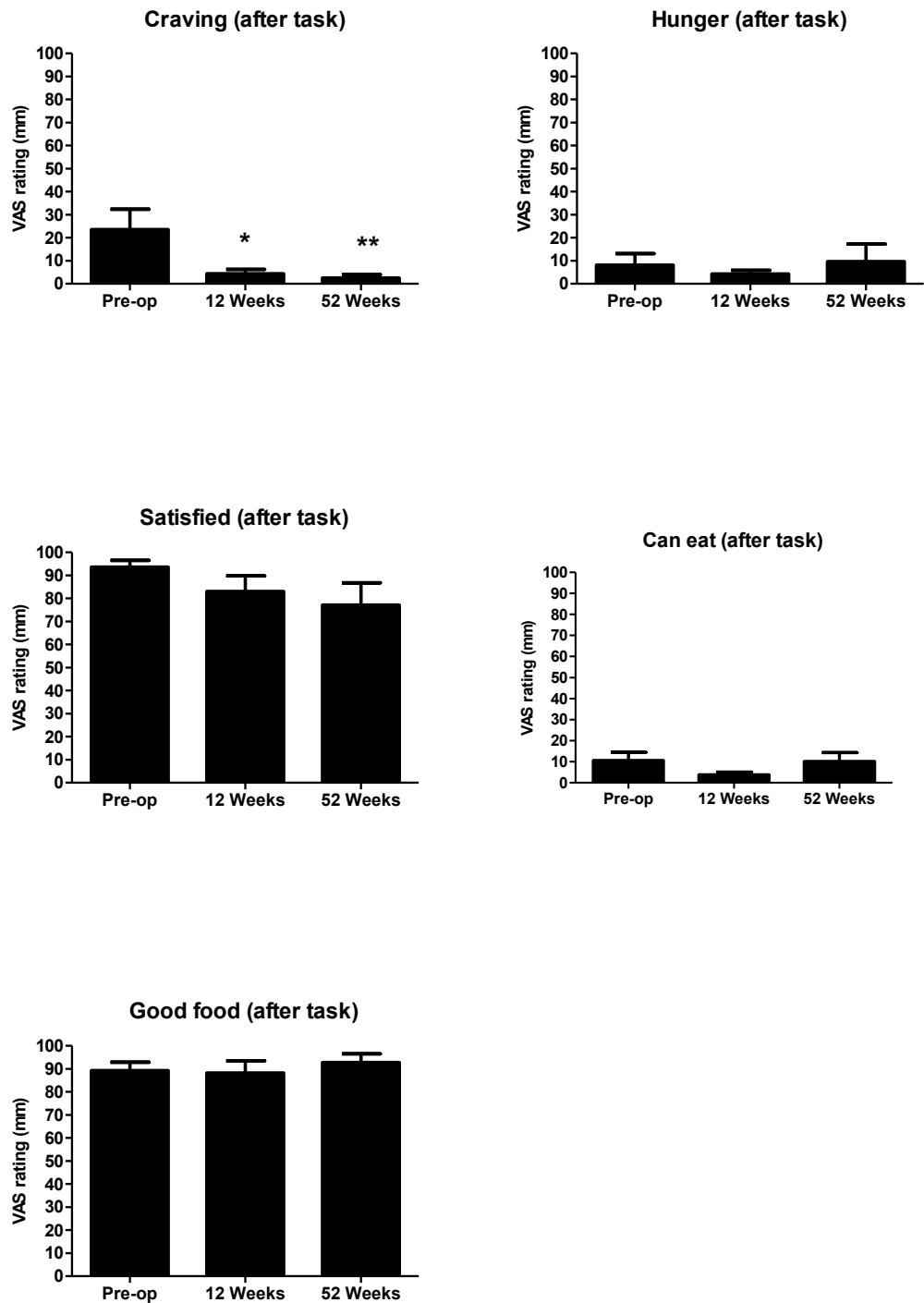
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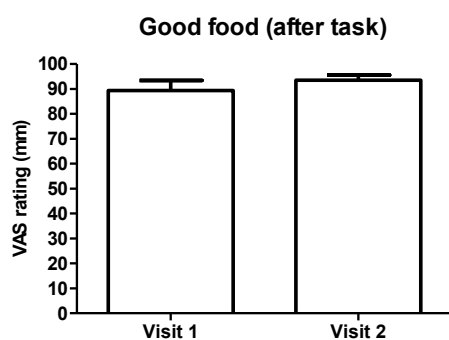
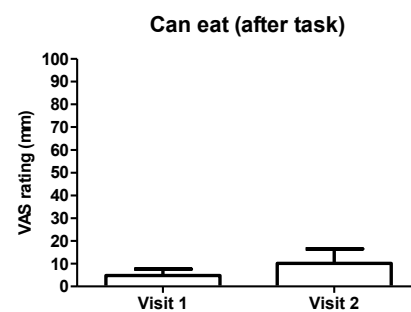
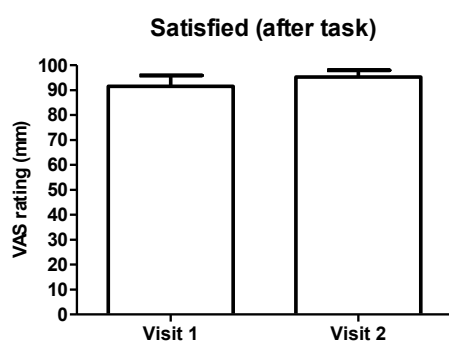
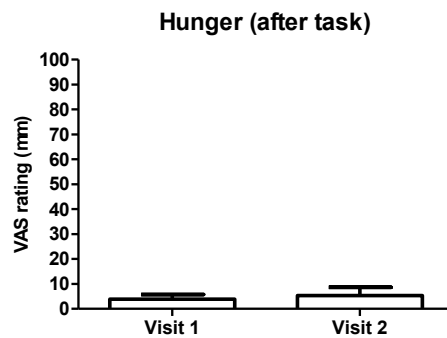
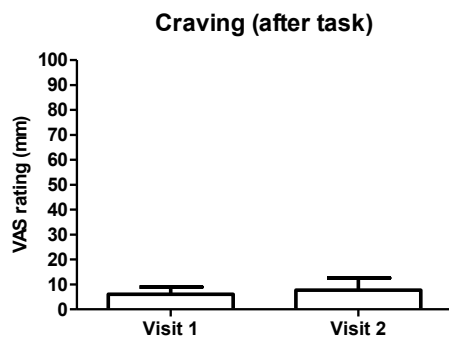




Appendix 5 Visual Analogue Scale Ratings for VSG and control subjects throughout interval visits

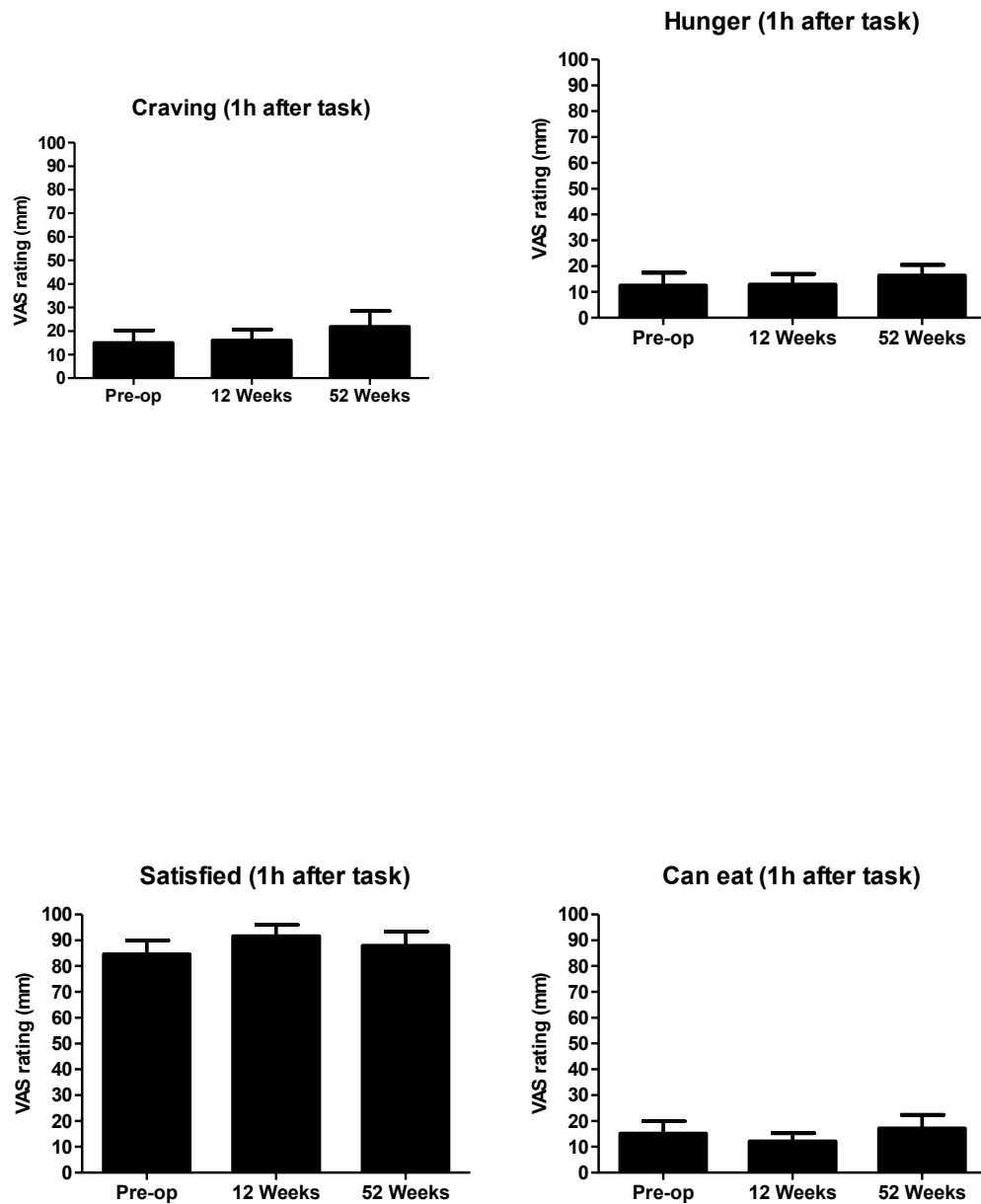
immediately after test meal

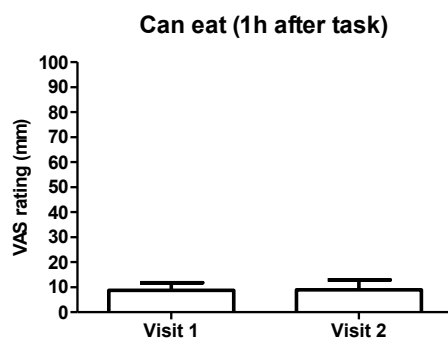
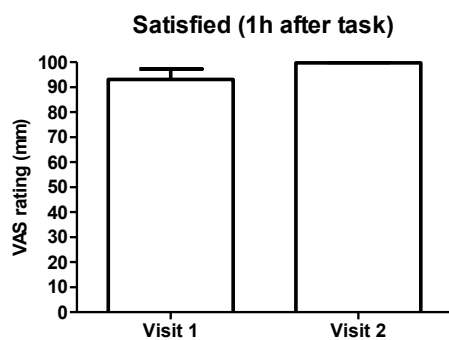
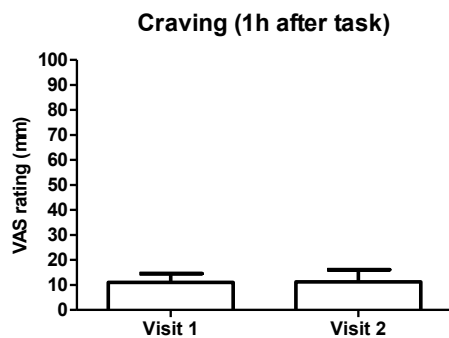




Appendix 6 Visual Analogue Scale Ratings for VSG and control subjects throughout interval visits 1

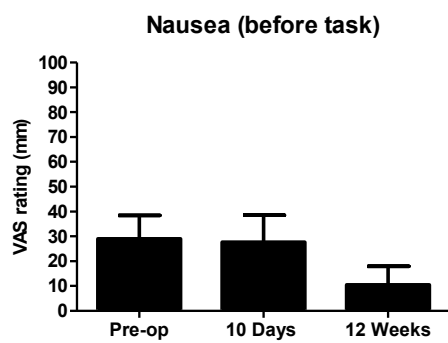
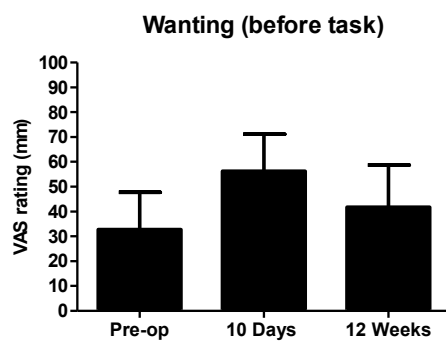
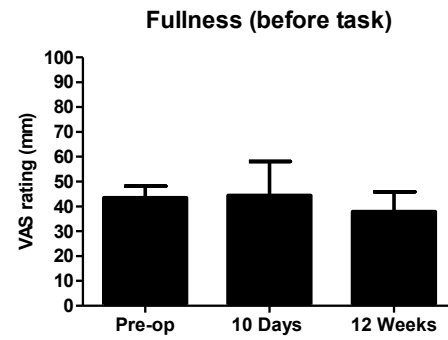
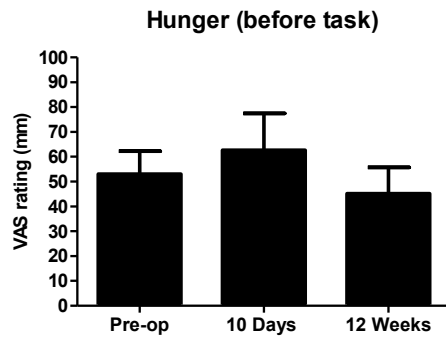
hour after the test meal

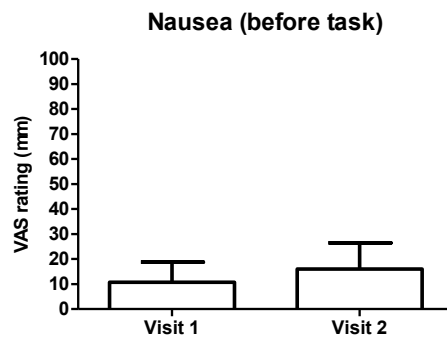
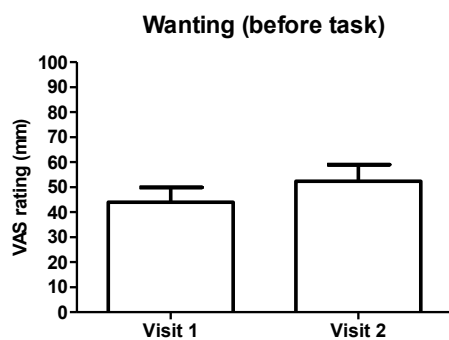
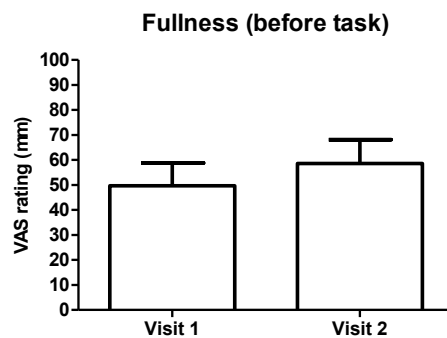
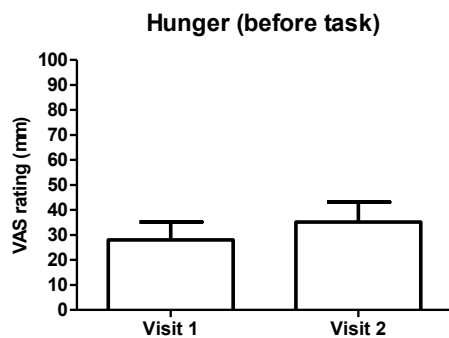




Appendix 7 Visual Analogue Scale Ratings for VSG and control subjects throughout interval visits

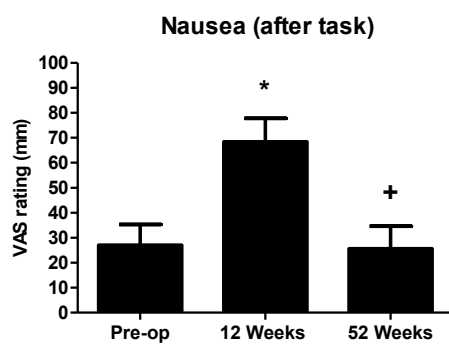
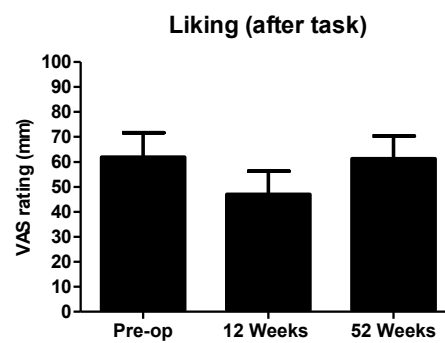
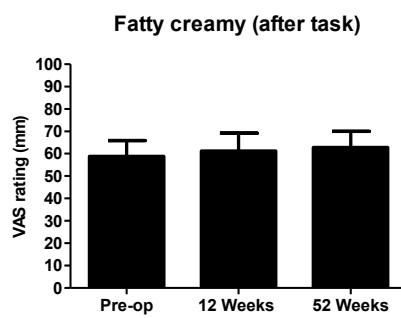
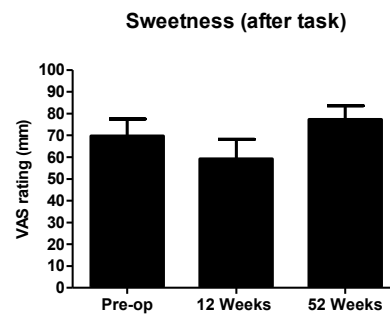
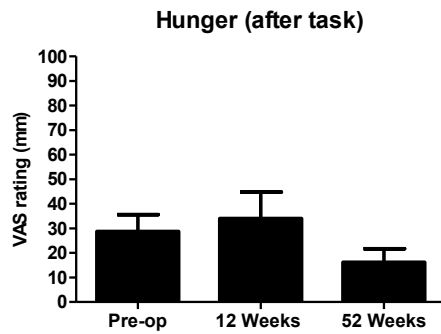
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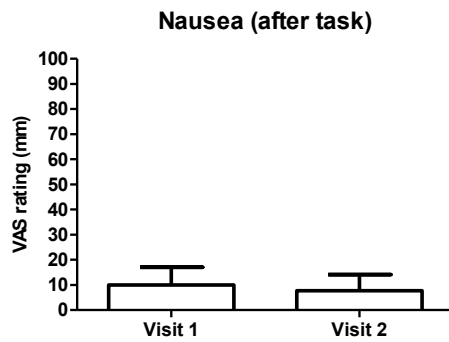
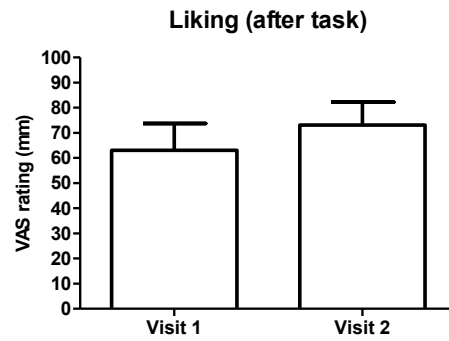
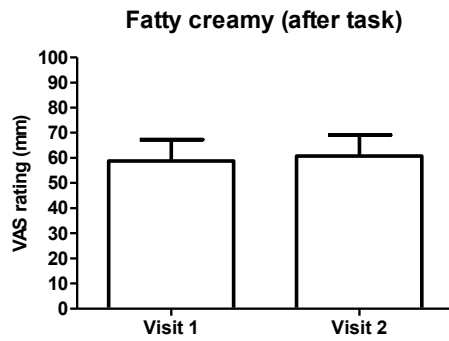




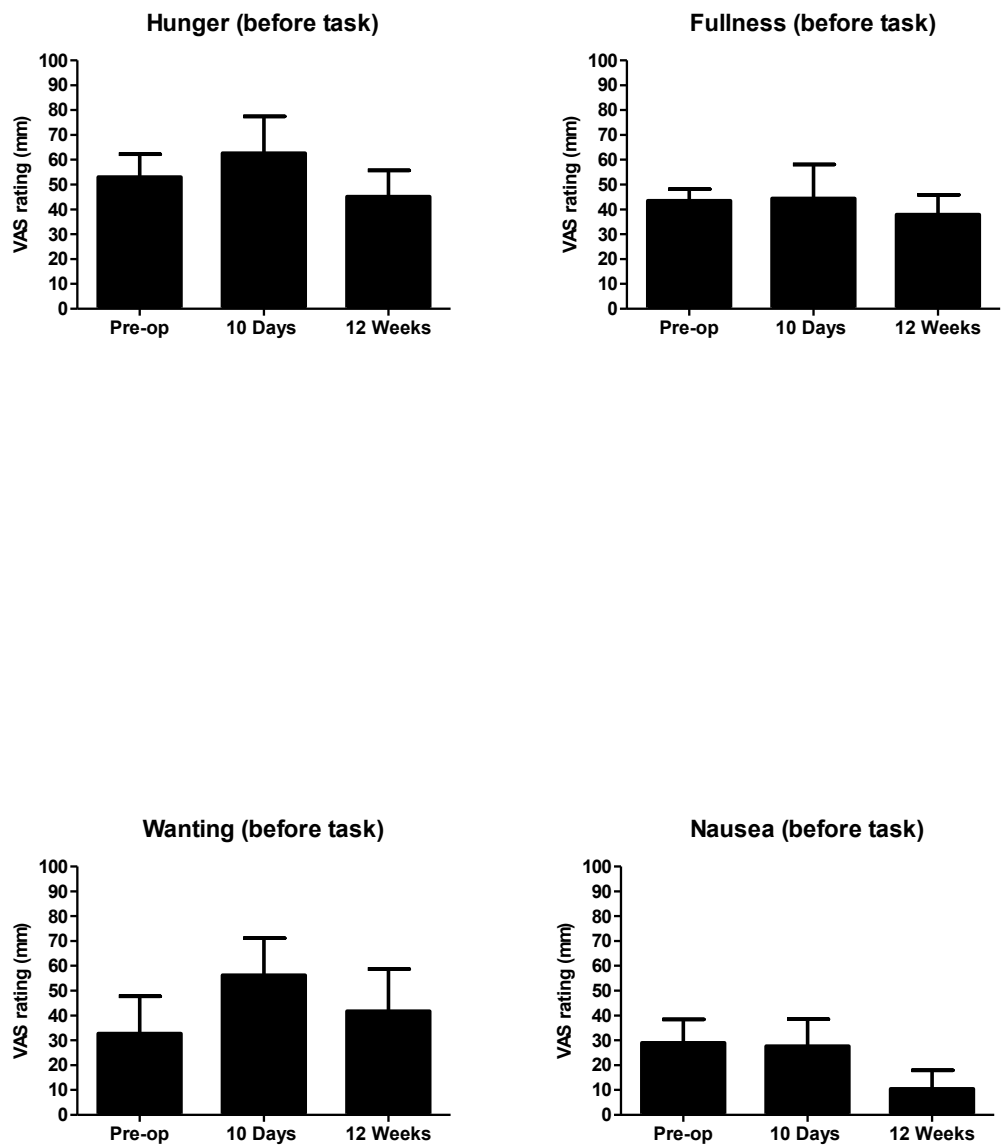
Appendix 8 Visual Analogue Scale Ratings for VSG and control subjects throughout interval visits

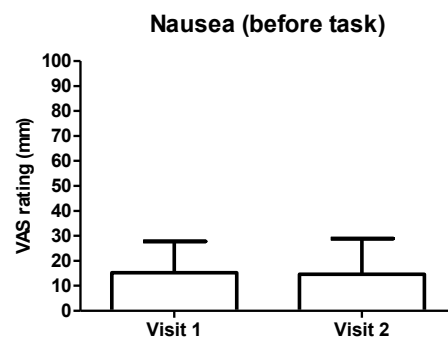
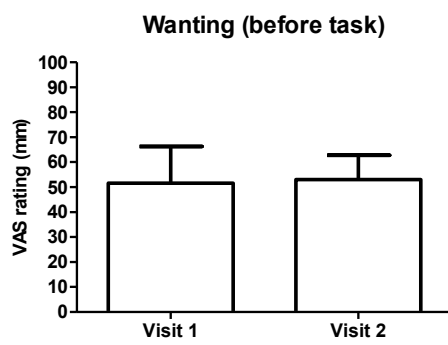
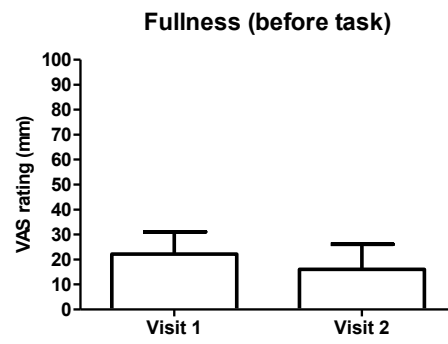
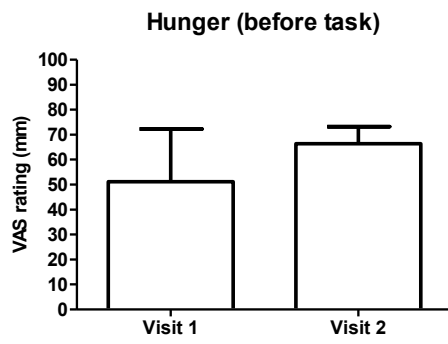
after PRT test



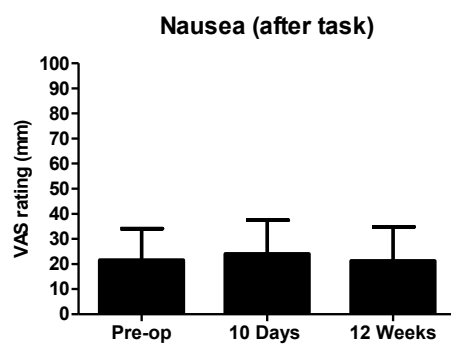
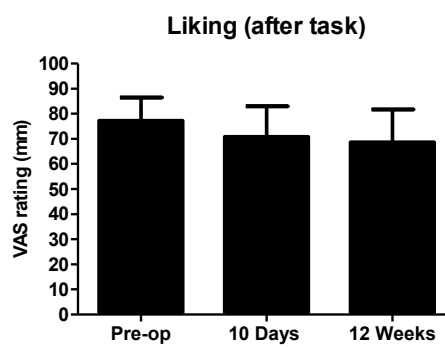
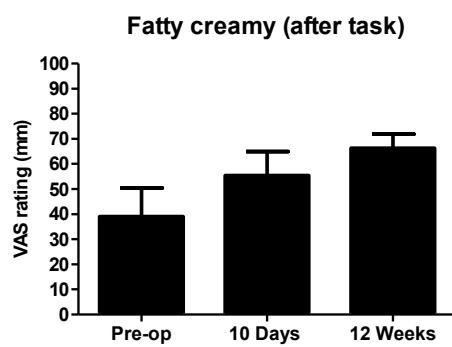
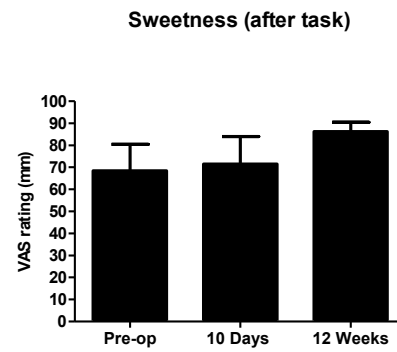
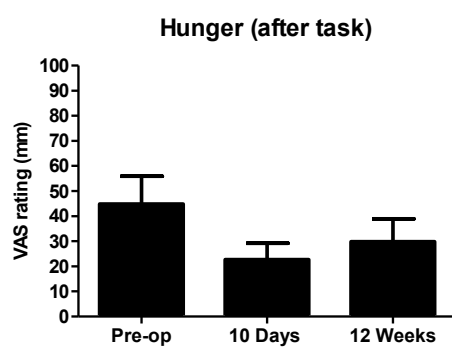


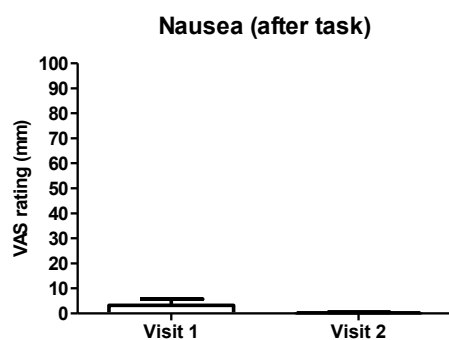
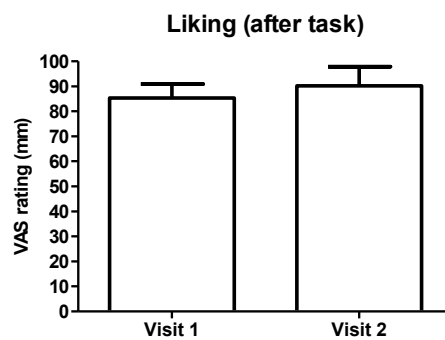
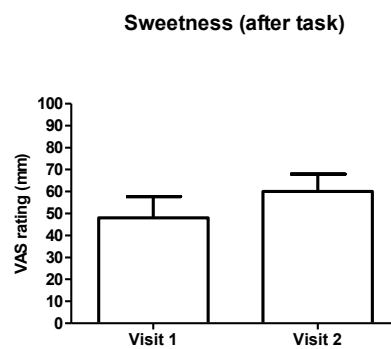
Appendix 9 Visual Analogue Scale Ratings for VSG and control subjects throughout interval visits before consummatory behaviour test



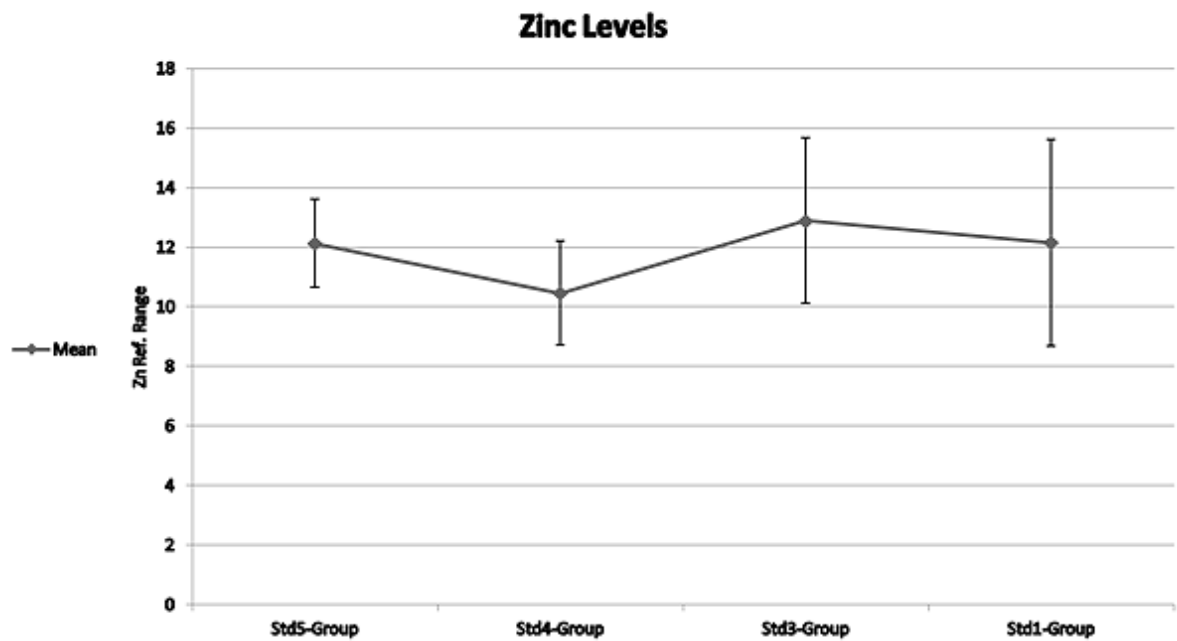


Appendix 10 Visual Analogue Scale Ratings for VSG and control subjects throughout interval visits
after consummatory behaviour test





Appendix 11 Normal Zinc levels for VSG subjects at baseline



Appendix 12 Chapter 3 Infra structure**Data Sheet – Eating behaviour and meal pattern study****Name:****Control / Subject****Code:****Type of Food:**

- 1- Beryani with Chicken (330 g); (Pro:30 g, Fat:8 g, Carb: 63 g, Kcal: 450)
- 2- Lasagne with meat (450 g); (Pro:32 g, Fat:13 g, Carb: 29 g, Kcal: 360)
- 3- Beef Burger (280 g); (Pro: 33.6 g, Fat: 14 g, Carb: 47.6 g, Kcal: 448)
- 4- Chicken Burger (265 g); (Pro: 34.5 g,Fat:15.9 g,Carb: 53 g, Kcal:503.5)
- 5- Shawarma Beef (220 g); (Pro:24.2 g, Fat:8.8 g, Carb: 44 g, Kcal: 330)
- 6- Shawarma Chicken (230 g); (Pro:25.3g,Fat:11.5g,Carb:48.3g,Kcal: 391)

Visit	Food Wt Before	Food Wt After	Start Time	Finish Time	Duration	Date
1 st	----- gm	----- gm	---:--- ...m	---:--- ...m	----- min	--/--/201
2 nd	----- gm	----- gm	---:--- ...m	---:--- ...m	----- min	--/--/201
3 rd	----- gm	----- gm	---:--- ...m	---:--- ...m	----- min	--/--/201



Meal Pattern lab setting pre-test



Eaten Food on weighing scale pre-test vs post-test with duration

Initials

Date / /

Visual Analogue Scale (pre-test)

HOW MUCH DO YOU CRAVE FOR EATING JUST NOW?

NOT AT ALL

EXTREMELY

HOW HUNGRY DO YOU FEEL RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW SATISFIED ARE YOU RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW MUCH FOOD COULD EAT RIGHT NOW?

NOTHING

A LARGE AMOUNT

Initials

Date / /

Visual Analogue Scale (post- test immediately)

HOW MUCH DO YOU CRAVE FOR EATING JUST NOW?

NOT AT ALL

EXTREMELY

HOW HUNGRY DO YOU FEEL RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW SATISFIED ARE YOU RIGHT NOW?

NOTHING

A LARGE AMOUNT

HOW MUCH FOOD COULD EAT RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW GOOD WAS THE FOOD?

NOT AT ALL

EXTREMELY

Why did you stop eating?

☐ I WAS FULL

☐ UNPLEASANT TASTE

☐ OTHER.....

Initials

Date / /

Visual Analogue Scale (1 hour post- test)

HOW MUCH DO YOU CRAVE FOR EATING JUST NOW?

NOT AT ALL

EXTREMELY

HOW HUNGRY DO YOU FEEL RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW SATISFIED ARE YOU RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW MUCH FOOD COULD EAT RIGHT NOW?

NOTHING

A LARGE AMOUNT

TEFQ-R21

This section contains statements and questions about eating habits and feelings of hunger.

Read each statement carefully and answer by ticking the alternative that best applies to you.

1. I deliberately take small helpings to control my weight

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

2. I begin eating when I feel anxious

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

3. Sometimes when I start eating, I just can't seem to stop

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

4. When I feel sad, I often eat too much

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

5. There are some foods I don't eat, because they make me fat

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

6. Being with someone who is eating, often makes me also wants to eat

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

7. When I feel tense or stressed, often feel I need to eat

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

8. I often feel so hungry that my stomach feels like a bottomless pit

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

9. I'm always so hungry that it's hard for me to stop eating before finishing all of the food on my plate

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

10. When I feel lonely, I console myself by eating

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

11. I consciously restrict how much I eat during meals to avoid gaining weight

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

12. When I smell appetizing food or see a delicious dish, I find it very difficult not to eat - even if I've just finished a meal

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

TEFQ-R21

This section contains statements and questions about eating habits and feelings of hunger.

Read each statement carefully and answer by ticking the alternative that best applies to you.

13. I am always sufficiently hungry to eat at any time

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

17. How often do you avoid "stocking up" on tempting foods?

- ☐ 1 Almost never
- ☐ 2 Rarely
- ☐ 3 Usually
- ☐ 4 Almost always

14. If I feel nervous, I try to calm myself down by Beating

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

18. How likely are you to make an effort to eat less than you want?

- ☐ 1 Unlikely
- ☐ 2 A little likely
- ☐ 3 Somewhat likely
- ☐ 4 Very likely

15. When I see something that looks delicious, it often makes me feel so hungry that I have to eat right away

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

19. Do you go on eating binges even though You're not hungry?

- ☐ 1 Never
- ☐ 2 Rarely
- ☐ 3 Sometimes
- ☐ 4 At least once a week

16. When I feel depressed, I want to eat

- ☐ 1 Definitely true
- ☐ 2 Mostly true
- ☐ 3 Mostly false
- ☐ 4 Definitely false

20. How often do you feel hungry?

- ☐ 1 Only at mealtimes
- ☐ 2 Sometimes between meals
- ☐ 3 Often between meals
- ☐ 4 Almost always

21. On a scale from 1 to 8, where 1 means no restraint in eating and 8 means constant restraint, what number would you give yourself?

Circle the number that best applies to you

1

2

3

4

5

6

7

8

I eat
whatever and
whenever I
want to

I am constantly
limiting my
food intake, never
"giving in"

24hrs recall methods Quetinnnaire

Name:

Code:

Date:

Day:

Time	Food or Beverage consumed	Amount

Food questionnaire (SOS)

For each food type, fill in your daily or weekly intake. Answer daily or weekly, not both. Choose a daily category if you eat the food daily, choose a weekly category if you don't eat the food daily. You can go back and forth between daily and weekly categories as often as necessary. All of your answers should describe your eating habits during the last 12 weeks.

VEGETARIAN/NON-VEGETARIAN?

- | | | | | | |
|----|---------------------------|-----|----|--------------------------|--------------------------|
| 1. | DO YOU EAT MEAT? | YES | NO | ☐ | ☐ |
| 2. | DO YOU EAT FISH? | YES | NO | ☐ | ☐ |
| 3. | DO YOU EAT MILK PRODUCTS? | YES | NO | ☐ | ☐ |
| 4. | DO YOU EAT EGGS? | YES | NO | ☐ | ☐ |

Bread

- | | | |
|----|--|--|
| 5. | HOW MANY PIECES OF BREAD DO YOU EAT? | Fill in one alternative |
| | Per day | (1) ☐ ☐ number |
| | Or | |
| | Per week | (2) ☐ ☐ number |
| 6. | HOW MANY PIECES OF CRISP BREAD DO YOU EAT? | Fill in one alternative |
| | Per day | (1) ☐ ☐ number |
| | Or | |
| | Per week | (2) ☐ ☐ number |

7. OUT OF 10 PIECES OF BREAD, ON HOW MANY DO YOU
USUALLY TAKE CHEESE, MEAT, And SAUSAGE OF LIVER
PÂTÉ ETC.?

Fill in 0 for toppings that you don't use

Cheese	(1)		number
Cottage cheese or Cheese spread	(2)		number
Meat, sausage or liver pâté	(3)		number
Swedish caviar, sardines, fish	(4)		number
Jam	(5)		number
Vegetables	(6)		number
Nothing	(7)		number

The sum should be: 10

8. HOW MUCH OF THE FOLLOWING DO YOU EAT? GIVE
THE AMOUNT IN NUMBER OF "NORMAL TOPPINGS
ON ONE SANDWICH"

1) Cheese

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

2) Cottage cheese or cheese Spread

Per day

(1) number

Or

Per week

(2) number

3) Meat, sausage or liver pâté

Per day

(1) number

Or

Per week

(2) number

4) Swedish caviar, sardine, fish

Per day

(1) number

Or

Per week

(2) number

5) Marmalade

Per day

(1) number

Or

Per week

(2) Number

9. OUT OF 10 PIECES OF BREAD, HOW MANY ARE:

Fill in 0 for toppings that you don't use

Rye, whole-wheat, or other

(1) number

Sweet Swedish bread

(2) number

White bread

(3) number

The sum should be: 10

10. HOW THICK ARE YOUR PIECES OF BREAD?

1) Brown bread

fill in a cross

Thinner than 1 cm

(1) number

Approximately 1 cm

(2) number

Thicker than 1 cm

(3) number

2) Sweet, Swedish bread

Thinner than 1 cm

Approximately 1 cm

Thicker than 1 cm

fill in a cross

(1) number

(2) number

(3) number

3) White bread

Thinner than 1 cm

Approximately 1 cm

Thicker than 1 cm

fill in a cross

(1) number

(2) number

(3) number

11. MUCH FAT DO YOU USUALLY SPREAD ON YOUR SANDWICHES?

Nothing

A thin layer

Normal layer

Thick layer

Very thick layer

fill in a cross

(1) number

(2) number

(3) number

(4) number

(5) number

12. OUT OF 10 PIECES OF BREAD, ON HOW MANY YOU USE:

Butter

A mixture of butter and oil

Margarine

Low fat margarine

No fat at all

Fill in 0 for the alternative you don't use

(1) number

(2) number

(3) number

(4) number

(5) number

The sum should be: 10

13. HOW MUCH OF THE FOLLOWING DO YOU EAT? GIVE
THE AMOUNT IN NUMBER OF "NORMAL TOPPINGS
ON ONE SANDWICH"

6) Cheese

Per day

Fill in one alternative

(1) number

Or

Per week

(2) number

7) Cottage cheese or cheese Spread

Per day

(1) number

Or

Per week

(2) number

8) Meat, sausage or liver pâté

Per day

(1) number

Or

Per week

(2) number

9) Swedish caviar, sardine, fish

Per day

(1) number

Or

Per week

(2) number

10) Marmalade

Per day

(1) number

Or

Per week

(2) Number

14. OUT OF 10 PIECES OF BREAD, HOW MANY ARE:

Fill in 0 for toppings that you don't use

Rye, whole-wheat, or other

(1) number

Sweet Swedish bread

(2) number

White bread

(3) number

The sum should be: 10

15. HOW THICK ARE YOUR PIECES OF BREAD?

4) Brown bread

fill in a cross

Thinner than 1 cm

(1) number

Approximately 1 cm

(2) number

Thicker than 1 cm

(3) number

5) Sweet, Swedish bread

fill in a cross

Thinner than 1 cm

(1) number

Approximately 1 cm

(2) number

Thicker than 1 cm

(3) number

6) White bread

fill in a cross

Thinner than 1 cm

(1) number

Approximately 1 cm

(2) number

Thicker than 1 cm

(3) number

16. MUCH FAT DO YOU USUALLY SPREAD ON YOUR SANDWICHES?

fill in a cross

Nothing

(1) number

A thin layer

(2) number

- | | | | |
|------------------|-----|---|--------|
| Normal layer | (3) | <input type="text"/> <input type="text"/> | number |
| Thick layer | (4) | <input type="text"/> <input type="text"/> | number |
| Very thick layer | (5) | <input type="text"/> <input type="text"/> | number |

17. OUT OF 10 PIECES OF BREAD, ON HOW MANY YOU USE: Fill in 0 for the alternative you don't use

- | | | | |
|-----------------------------|-----|---|--------|
| Butter | (1) | <input type="text"/> <input type="text"/> | number |
| A mixture of butter and oil | (2) | <input type="text"/> <input type="text"/> | number |
| Margarine | (3) | <input type="text"/> <input type="text"/> | number |
| Low fat margarine | (4) | <input type="text"/> <input type="text"/> | number |
| No fat at all | (5) | <input type="text"/> <input type="text"/> | number |

The sum should be: 10

BEVERAGES

18. HOW MUCH DO YOU CONSUME OF THE FOLLOWING? (INCLUDING MILK PRODUCTS ON CEREAL)

Fill in 0 per week for those you don't use

1) Whole milk

Glass (250ml) per day

Or

Glass (250ml) per week

Fill in one alternative

(1) number

(2) number

2) Low fat milk (1%)

Glass (250ml) per day

Or

Glass (250ml) per week

Fill in one alternative

(1) number

(2) number

3) Skim milk

Glass (250ml) per day

Or

Glass (250ml) per week

Fill in one alternative

(1) number

(2) number

4) Yoghurt/fermented milk (whole)

Glass (250ml) per day

Or

Glass (250ml) per week

Fill in one alternative

(1) number

(2) number

5) Low fat yoghurt

Glass (250ml) per day

Or

Glass (250ml) per week

Fill in one alternative

(1) number

(2) number

6) Juice

Glass (250ml) per day

Or

Glass (250ml) per week

Fill in one alternative

(1) number

(2) number

7) Fruit drink, soft drink

Glass (250ml) per day

Or

Glass (250ml) per week

Or

Bottles/Cans per day

Or

Bottles/Cans per week

Fill in one alternative

(1) number

(2) number

(3) number

(4) number

8) Alcohol-free beer

Fill in one alternative

Glass (250ml) per day

(1) number

Or

Glass (250ml) per week

(2) number

Or

Bottles/Cans per day

(3) number

Or

Bottles/Cans per week

(4) number

9) Energy Drinks

Fill in one alternative

Glass (250ml) per day

(1) number

Or

Glass (250ml) per week

(2) number

Or

Bottles/Cans per day

(3) number

Or

Bottles/Cans per week

(4) number

FRUITS

19. HOW MUCH CITRUS FRUIT (ORANGES, LEMONS,
TANGERINES, AND GRAPEFRUITS) DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

20. HOW MANY APPLES/PEARS DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

21. HOW MANY BANANAS DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

22. HOW MANY PORTIONS OF GRAPES DO YOU EAT?
(One portion of about 15-20 grapes are approx.
100g)

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

23. HOW MANY PLUMS DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

24. HOW MANY PORTIONS OF MELON DO YOU EAT PER
WEEK?

Per week

number of portions

25. HOW MANY PEACHES/NECTARINES YOU EAT?

Per week

number

26. HOW MANY PORTIONS OF EXOTIC FRUITS (KIWI,
PAPAYA, MANGO, and PINEAPPLE) DO YOU EAT?

Per week

number of portions

CAKES AND COOKIES

27. MANY (LIST OF SEWDISH NAMES FOR HIGH-FAT,
HIGH SUGAR CAKES) DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

28. HOW MANY SWEET BUNS AND (SWEDISH NAMES)
FOR SWEDISH CAKE DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

29. HOW MANY COOKIES AND BISCUITS AND SUCH
DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

DESSERTS AND SNACKS

30. HOW MANY FRUIT DESSERTS DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

31. HOW MUCH ICE CREAM DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

32. HOW MUCH PIE, PUDDING, CHOCOLATE MOUSSE,
AND SUCH DO YOU EAT?

Per day

(1) number

Or

Per week

(2) number

EGGS

33. HOW MANY EGGS DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

PORRIDGE GRUEL AND BREAKFAST CEREAL

34. HOW MANY PORTIONS OF PORRIDGE DO YOU
EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

35. HOW MANY PORTIONS OF GRUEL DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

36. HOW MANY PORTIONS OF CEREAL DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

LIGHT MEALS

With light meals we mean omelet's, soup, salad, cottage cheese, hot sandwiches etc. Do not include cereals and full lunches here.

32a. HOW MANY LIGHT MEALS DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) Number

OTHER FAST FOODS

32b. HOW MANY HAMBURGERS, HOT DOGS WITH
BREAD OR FRIES DO YOU EAT?

Fill in one alternative

Per week

(1) number

32c. HOW MANY PIZZAS DO YOU EAT?

Per week

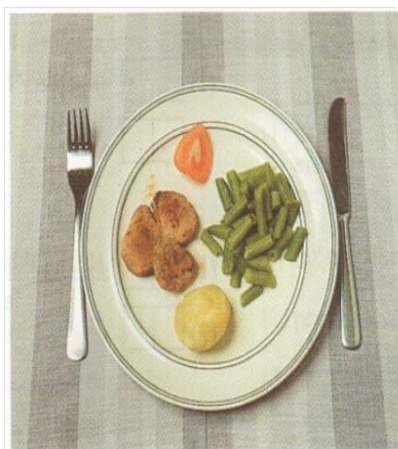
(1) Number

MAIN MEALS

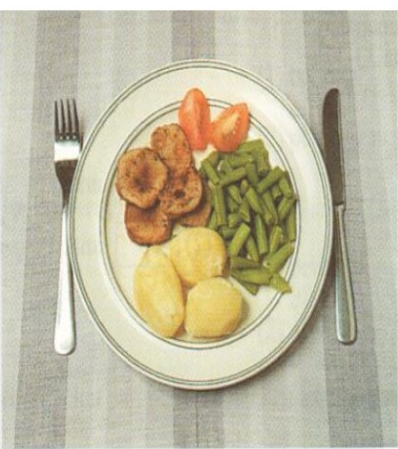
'Main meals' refer to hot lunches, dinners, or any main meal, even if eaten during a night shift).

EXAMPLE OF PROTION SIZES

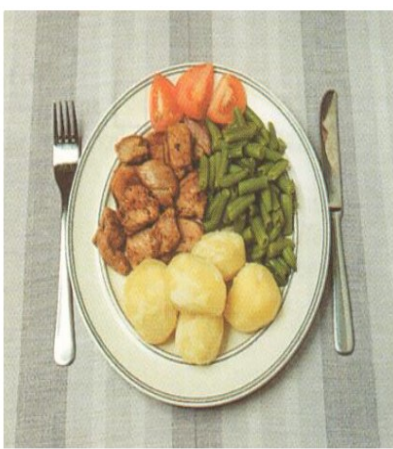
Attention! Do not include porridge, light meals or pizza here, since you have already described them.



Portion A



Portion B



Portion C

33. HOW MANY SUCH MEALS DO YOU EAT ON

MONDAY, TUESDAY, WEDNESDAY AND

Fill in one alternative

THURSDAY?

Main meals per day

(1) number

OR

Main meals per 4 days

(2) number

Look at the picture on the previous page. As you see they are various sizes describe your own portion sizes in relation to the picture. You can choose potatoes from one portion, meat from another and vegetable from a third.

1) *Potatoes, rice, spaghetti etc.* in your main meals on Mondays -Thursdays? Check the alternative that best describes the average portion size on most days.

ONE CROSS

- | | | |
|----------------------------|------|--------------------------|
| I don't eat it | (1) | ☐ |
| Half of portion A | (2) | ☐ |
| Same as Portion A | (3) | ☐ |
| Between portion A and B | (4) | ☐ |
| Same as Portion B | (5) | ☐ |
| Between portion B and C | (6) | ☐ |
| Same as Portion C | (7) | ☐ |
| Twice as much as portion C | (8) | ☐ |
| Three times as portion C | (9) | ☐ |
| Four times as portion C | (10) | ☐ |

2) *Meat, Fish, fowl, and seafood* on average on Mondays -Thursdays if you are a vegetarian relate the meat portion shown here to your vegetarian alternatives (soy beans, lentils, beans etc.)

ONE CROSS

- | | | |
|-------------------------|-----|--------------------------|
| I don't eat it | (1) | ☐ |
| Half of portion A | (2) | ☐ |
| Same as Portion A | (3) | ☐ |
| Between portion A and B | (4) | ☐ |
| Same as Portion B | (5) | ☐ |
| Between portion B and C | (6) | ☐ |

- | | | |
|----------------------------|------|--------------------------|
| Same as Portion C | (7) | ☐ |
| Twice as much as portion C | (8) | ☐ |
| Three times as portion C | (9) | ☐ |
| Four times as portion C | (10) | ☐ |

3) *Vegetables* on average per main meal Monday-Thursday

ONE CROSS

- | | | |
|----------------------------|------|--------------------------|
| I don't eat it | (1) | ☐ |
| Half of portion A | (2) | ☐ |
| Same as Portion A | (3) | ☐ |
| Between portion A and B | (4) | ☐ |
| Same as Portion B | (5) | ☐ |
| Between portion B and C | (6) | ☐ |
| Same as Portion C | (7) | ☐ |
| Twice as much as portion C | (8) | ☐ |
| Three times as portion C | (9) | ☐ |
| Four times as portion C | (10) | ☐ |

34. HOW MANY MAIN MEALS DO YOU EAT ON FRIDAYS?

Main meals on Fridays ☐ number

Describe the size of your main meal on Friday in relation to the pictures.

.....

1) *Potatoes, rice, spaghetti etc.* in your main meals on Mondays -Thursdays? Check the alternative that best describes the average portion size on most days.

ONE CROSS

- | | | |
|----------------------------|------|--------------------------|
| I don't eat it | (1) | ☐ |
| Half of portion A | (2) | ☐ |
| Same as Portion A | (3) | ☐ |
| Between portion A and B | (4) | ☐ |
| Same as Portion B | (5) | ☐ |
| Between portion B and C | (6) | ☐ |
| Same as Portion C | (7) | ☐ |
| Twice as much as portion C | (8) | ☐ |
| Three times as portion C | (9) | ☐ |
| Four times as portion C | (10) | ☐ |

2) *Meat, Fish, fowl, and seafood* on average on Mondays -Thursdays if you are a vegetarian relate the meat portion shown here to your vegetarian alternatives (soy beans, lentils, beans etc.)

ONE CROSS

- | | | |
|----------------------------|-----|--------------------------|
| I don't eat it | (1) | ☐ |
| Half of portion A | (2) | ☐ |
| Same as Portion A | (3) | ☐ |
| Between portion A and B | (4) | ☐ |
| Same as Portion B | (5) | ☐ |
| Between portion B and C | (6) | ☐ |
| Same as Portion C | (7) | ☐ |
| Twice as much as portion C | (8) | ☐ |

Three times as portion C (9) ☐

Four times as portion C (10) ☐

3) *Vegetables* on average per main meal Monday-Thursday

ONE CROSS

I don't eat it (1) ☐

Half of portion A (2) ☐

Same as Portion A (3) ☐

Between portion A and B (4) ☐

Same as Portion B (5) ☐

Between portion B and C (6) ☐

Same as Portion C (7) ☐

Twice as much as portion C (8) ☐

Three times as portion C (9) ☐

Four times as portion C (10) ☐

35. HOW MANY COOKED MEALS DO YOU EAT ON

SATURDAY AND SUNDAY?

total of all main meals during these 2 days number

Describe your main Saturday and Sunday meal sizes in relation to the pictures.

.....

1) *Potatoes, rice, spaghetti etc.* in your main meals on Mondays -Thursdays? Check the alternative that best describes the average portion size on most days.

ONE CROSS

- | | | |
|----------------------------|------|--------------------------|
| I don't eat it | (1) | ☐ |
| Half of portion A | (2) | ☐ |
| Same as Portion A | (3) | ☐ |
| Between portion A and B | (4) | ☐ |
| Same as Portion B | (5) | ☐ |
| Between portion B and C | (6) | ☐ |
| Same as Portion C | (7) | ☐ |
| Twice as much as portion C | (8) | ☐ |
| Three times as portion C | (9) | ☐ |
| Four times as portion C | (10) | ☐ |

2) *Meat, Fish, fowl, and seafood* on average on Mondays -Thursdays if you are a vegetarian relate the meat portion shown here to your vegetarian alternatives (soy beans, lentils, beans etc.)

ONE CROSS

- | | | |
|----------------------------|-----|--------------------------|
| I don't eat it | (1) | ☐ |
| Half of portion A | (2) | ☐ |
| Same as Portion A | (3) | ☐ |
| Between portion A and B | (4) | ☐ |
| Same as Portion B | (5) | ☐ |
| Between portion B and C | (6) | ☐ |
| Same as Portion C | (7) | ☐ |
| Twice as much as portion C | (8) | ☐ |

Three times as portion C (9) ☐

Four times as portion C (10) ☐

3) *Vegetables* on average per main meal Monday-Thursday

ONE CROSS

I don't eat it (1) ☐

Half of portion A (2) ☐

Same as Portion A (3) ☐

Between portion A and B (4) ☐

Same as Portion B (5) ☐

Between portion B and C (6) ☐

Same as Portion C (7) ☐

Twice as much as portion C (8) ☐

Three times as portion C (9) ☐

Four times as portion C (10) ☐

36. IMAGINE 10 CONSECUTIVE MAIN MEALS APPROXIMATELY HOW MANY CONSIST OF THE FOLLOWING?

Fill in 0 for food types that you don't use no. of meals

Soy burgers, lentils, beans etc. (1) ☐☐

Beef, ground meat, pork chop, filet, chicken, other

fowl, game (2) ☐☐

Fish, seafood (3) ☐☐

Salted pork, bacon, sausage, other Fatty meals (4) ☐☐

The sum should be: 10

37. IMAGINE 10 CONSECUTIVE MAIN MEALS

APPROXIMATELY HOW MANY OF THESE MEALS ARE: no. of meals

Boiled (1)

Fried (2)

The sum should be: 10

38. IMAGINE 10 KG OF FAT USED IN YOUR HOUSEHOLD

FOR COOKING (EXCLUDING SANDWICH SPREAD) HOW

DO THESE 10 KILOS DIVIDE OUT?

Fill in 0 for cooking fat that you don't use no. of Kg

Butter (1)

A mixture of butter and oil (2)

Margarine (3)

light margarine (4)

Oil (5)

The sum should be: 10

Candy

39. HOW MANY CHOCOLATE BARS (NORMAL SIZE 100g)

Fill in one alternative

DO YOU EAT?

Per day (1) number

Or

Per week (2) number

40. HOW MANY LARGE CHOCOLATE BARS (250g) DO YOU

Fill in one alternative

EAT? (same size as cooking chocolate bars)

Per day (1) number

Or

Per week

(2) number

41. HOW MANY CHOCOLATE BARS (MARS, SNEAKERS
ETC.) DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

42. HOW MANY PIECES OF CHOCOLATE (BOX-TYPE) YOU
EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

43. MANY NON-CHOCOLATE SWEETS DO YOU EAT?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

44a. HOW MANY CANDIES OR EQUIVALENTS DO YOU EAT?

Fill in one alternative

100 g per day

(1) number

Or

100 g per week

(2) number

Or

small bag daily

(3) number

Or

small bag weekly

(4) number

Or

big bag daily

(5) number

If we have not included all types of candies that you eat, fill in the category (39-44) that is the most similar in such a way that the total number of candies eaten per day or week is approximately correct.

45. HOW MANY NUTS, PRETZELS DO YOU EAT?

Fill in one alternative

Small bag of (approx. 125g) per day

(1) number

Small bag of (approx. 125g) per week

(2) number

big bag of (approx. 130g) per day

(3) number

big bag of (approx. 125g) per week

(4) number

46. HOW MANY CHIPS CHEESE PUFFS ETC. DO YOU EAT?

Fill in one alternative

1 large bag per day

(1) number

Or

1 large bag per week

(2) number

Or

1 small bag per day

(3) number

Or

1 small bag per week

(4) number

COFFEE, TEA, HOT (OR COLD) CHOCOLATE DRINK

47. HOW MANY CUPS OF COFFEE DO YOU DRINK?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

How many sugar cubes do you use in a cup of coffee?

number

Do you put anything else on your coffee?

ONE CROSS

No

(1) ☐

yes, whipping cream

(2) ☐

yes, half and half

(3) ☐

yes, milk

(4) ☐

48. HOW MANY CUPS OF TEA DO YOU DRINK?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

How many sugar cubes do you put in a cup of tea?

number

49. HOW MANY CUPS OF HOT (OR COLD) CHOCOLATE DO
YOU DRINK?

Fill in one alternative

Per day

(1) number

Or

Per week

(2) number

Which liquids do you use for making chocolate drink?

ONE CROSS

Water

(1) ☐

Milk

(2) ☐

cream and water

(3) ☐

cream and milk

(4) ☐

Appendix 13 Chapter 4 Infra structure



Taste Detection test lab setting



Taste Detection preparation phase

PRESENTATION ORDER (Disterbution of stemulants and water in cups in 8 blocks randomly)

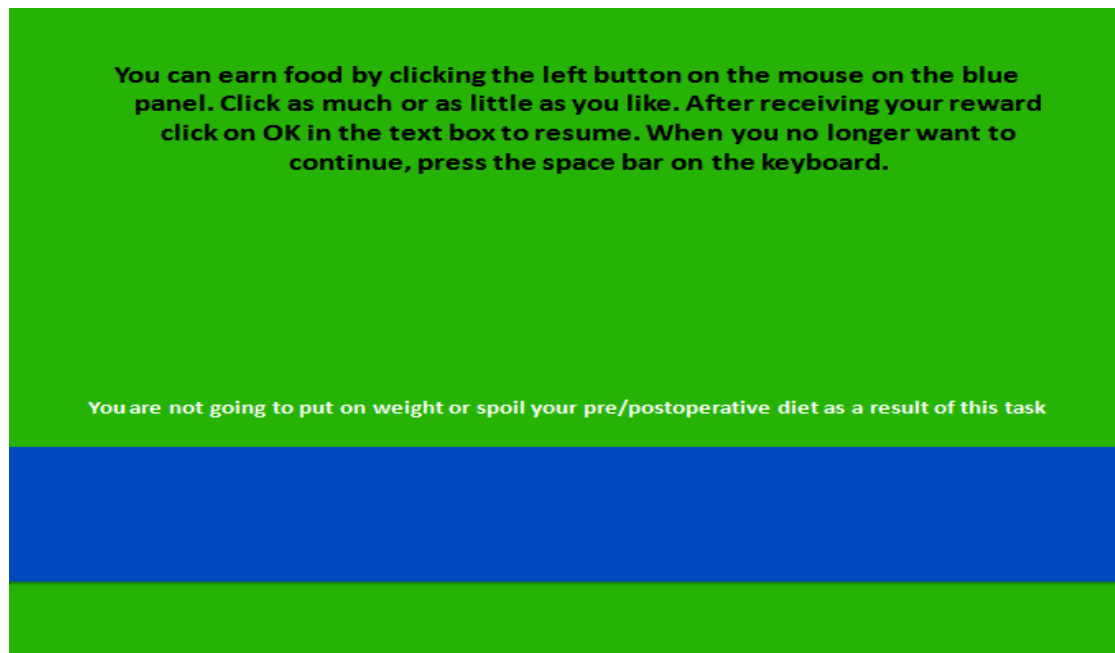
B 1 (T1-14)	S6	S1	w	S5	w	S3	w	S4	w	S2	W	w	S7	w
B 2 (T15-28)	S6	w	w	S4	w	S3	w	S7	w	S5	S1	w	S2	w
B 3 (T29-42)	W	S7	w	w	S2	S5	S6	w	S4	w	W	S3	S1	w
B 4 (T43-56)	S3	w	S2	S6	w	W	S7	w	w	w	S1	w	S4	S5
B 5 (T57-70)	W	S3	S2	w	S1	S7	w	S5	S6	w	S4	w	w	w
B 6 (T71-84)	W	S6	w	S5	w	S4	S1	w	w	w	S7	w	S3	S2
B 7 (T85-98)	W	S5	w	w	S2	W	S3	w	S6	S1	W	S4	w	S7
B 8 (T99-112)	S1	S6	w	S5	S7	W	w	w	w	S2	S3	w	S4	w

- A. The probability of receiving a water trial is 0.5. Thus half of the cups will contain water.
- B. Each taste compound will be tested in 12 blocks (B1-B12). A block of trials will consist of 7 tastes (S1-S7) and 7 distilled water trials (w) presented in random order without replacement. Each concentration (from 7) will be presented once within a block.

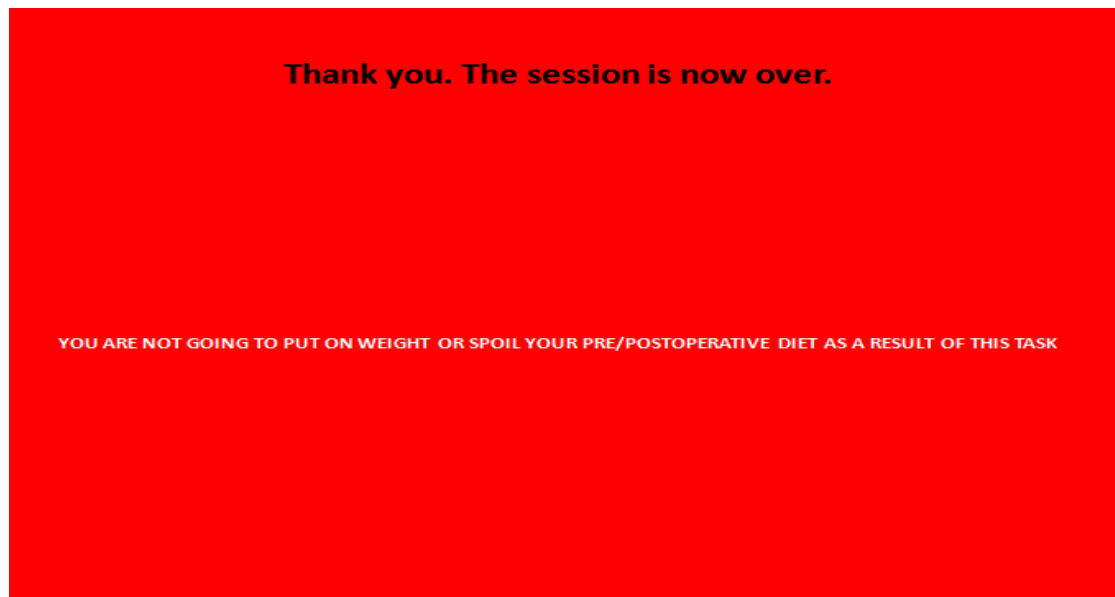
Appendix 14 Chapter 5 Infra structure



Lab setting and Sleeve subject performing the PRT test (consent obtained)



Progressive Ratio Task Program (Test screen)



Progressive Ratio Task Program (Termination test screen)

Initials

Date /..... /.....

Visual Analogue Scale (pre – test)

HOW HUNGRY DO YOU FEEL RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW FULL DO YOU FEEL RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW MUCH DO YOU WANT THE M&M?

NOTHING

A LARGE AMOUNT

HOW SICK/NAUSEATED DO YOU FEEL?

NOT AT ALL

EXTREMELY

What did you have for breakfast and how much?

.....

.....

Initials

Date /..... /.....

Visual Analogue Scale (post – test)

HOW HUNGRY DO YOU FEEL RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW SWEET WAS THE M&M?

NOT AT ALL

EXTREMELY

HOW FATTY/CREAMY WAS THE M&M?

NOTHING

A LARGE AMOUNT

HOW MUCH DID YOU LIKE THE M&M?

NOT AT ALL

EXTREMELY

HOW SICK/NAUSEATED DO YOU FEEL?

NOT AT ALL

EXTREMELY

WHY DID YOU STOP PRESSING THE BUTTON?

☐ FEEL FULL

☐ UNPLEASANT TASTE

☐ FEEL SICK

☐ OTHER

Appendix 15 Chapter 6 Infra structure



Setting and preparation of Consummatory behaviour test with control volunteer picture (consent obtained) * Permission was obtained from the child's parents to show his eyes.

Initials

Date / /

Visual Analogue Scale (Pre-test)

HOW HUNGRY DO YOU FEEL RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW FULL DO YOU FEEL RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW MUCH DO YOU THINK YOU COULD EAT RIGHT NOW?

NOTHING

A LARGE AMOUNT

HOW SICK/NAUSEATED DO YOU FEEL?

NOT AT ALL

EXTREMELY

What did you have for breakfast and how much?

.....

Initials

Date / /

Visual Analogue Scale (Post-test)

HOW HUNGRY DO YOU FEEL RIGHT NOW?

NOT AT ALL

EXTREMELY

HOW SWEET WAS THE MILKSHAKE?

NOT AT ALL

EXTREMELY

HOW FATTY/CREAMY WAS THE MILKSHAKE?

NOTHING

A LARGE AMOUNT

HOW MUCH DID YOU LIKE THE MILKSHAKE?

NOT AT ALL

EXTREMELY

HOW SICK/NAUSEATED DO YOU FEEL?

NOT AT ALL

EXTREMELY

Facial Expression Food Preference Rating Scale, Like vs. Dislike of Standardized Tastent

Directions: Rate the following items according to the frequency of occurrence. Use the following guidelines for your ratings:

- 0 Never observed-You have never seen the individual behave in this manner.
- 1 Seldom Observed-Individual behaves in this manner for about (1-2) of the time.
- 2 Sometimes Observed-Individual behaves in this manner for about (3-4) of the time.
- 3 Frequently observed-Individual behaves in this manner for about (≥ 5) of the time.

Circle the number that best describes your observations of the individual's typical behaviour under this certain circumstances. Remember to rate every item, If you are uncertain about how to rate an item delay the rating and repeat and pause the video. REMEMBER, EVERY ITEM SHOULD RECEIVE A SCORE.

Food Preference Behaviour	Never Observed	Seldom Observed	Sometimes Observed	Frequently Observed	Frequency
General Behaviours					
-Body movement	0	1	2	3	
-Hand movement	0	1	2	3	
-Head movement	0	1	2	3	
-Eye movement	0	1	2	3	
-Up	0	1	2	3	
-Down	0	1	2	3	
-Right	0	1	2	3	

-Left	0	1	2	3	
-Looking to the stimuli	0	1	2	3	
-Turn off the stimuli flow	0	1	2	3	
-Overall calmness	0	1	2	3	
Facial Expression: Positive Or Negative Effective Values					
Negative effective values:					
Upper Face:					
-Inner eyebrows raised	0	1	2	3	
-outer eyebrows raised	0	1	2	3	
-Browed pulled together and lowered	0	1	2	3	
-Nose wrinkle	0	1	2	3	
-eye closed	0	1	2	3	
-blink	0	1	2	3	
-Cheek raiser(neutral)	0	1	2	3	
Lower Face:					
-Upper lip raiser	0	1	2	3	
-Lip corner depressor	0	1	2	3	
-Lip stretch	0	1	2	3	
-Lip pressed	0	1	2	3	
-Lips part	0	1	2	3	
-Gape	0	1	2	3	
Positive effective values:					
Upper Face:					

-Smile with cheeks raised	0	1	2	3	
-Cheek raise (neutral)	0	1	2	3	
Lower Face:					
-Lip corner puller	0	1	2	3	
-Smile with open mouth	0	1	2	3	
-Lip smack	0	1	2	3	
-Chin raiser (neutral)	0	1	2	3	
-Lip pucker (neutral)	0	1	2	3	
Gross Behaviour:					
Neutral face (neutral)	0	1	2	3	
Lip bite (neutral)	0	1	2	3	
Head shake (negative)	0	1	2	3	
Head nod (positive)	0	1	2	3	
Tongue protrusion (positive)	0	1	2	3	
Cheek sucking (positive)	0	1	2	3	
Subtotals	-	-	-	-	
	+	+	+	+	
Behaviours Total Raw Score					