Identification of Factors Predictive of Outcome following Roux-en-Y Gastric Bypass for Obesity

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Abstract

INTRODUCTION: Worldwide obesity levels have doubled since 1980. Bariatric surgery is the only effective long-term treatment however its results remain highly patient, procedure and surgeon dependent. This study aimed to assess the impact of a range of factors on the outcome of Roux-en-Y gastric bypass (RYGBP) surgery. METHOD: All patients eligible for RYGBP at 2 regional centres were approached for inclusion. Data pertaining to 13 factors identified as potentially associated with reduction in excess BMI (eBMI) following RYGBP were collected: genetic predisposition to obesity, ethnicity, reasons for seeking surgery, eating behaviour, physical activity level, quality of life, personality score, motivation to change, alcohol intake, smoking history, social class, working pattern and past medical history. The data were analysed using multivariate linear and logistic regression analysis. The primary outcome was the percentage eBMI loss at 12 months postoperatively. The secondary outcomes were the resolution of diabetes and/ or hypertension. RESULTS: 129 patients were recruited after written informed consent of whom just 60 were eligible for analysis. At 12 months postoperatively their percent eBMI losses ranged between 33.4% and 136.2% (mean 67.3%, SD 18.8%). Of the 13 factors investigated using linear regression none showed a significant correlation with percent eBMI loss. Logistic regression analysis showed that personality score, motivation to change score and smoking status were all significantly associated with eBMI loss of 70% or greater when combined with the other investigated factors ($p = 0.013$, $p = 0.016$ and $p = 0.027$ respectively) but not when analysed individually. 9 out of 12 (75%) and 5 out of 14 (35.7%) patients on medication preoperatively for type 2 diabetes mellitus and hypertension respectively were able to discontinue their medication by 12 months post-RYGBP. CONCLUSIONS: This pilot study shows that a multi-factorial approach to clinical prediction and patient selection is viable and feasible.

Table of Contents

List of Tables and Figures

List of Appendices

Dedication and Acknowledgements

This work is dedicated to my family. Without the support of my wonderful wife Nicky and my parents I would never have been able to finish it. Thanks too go to my beautiful daughters Izzy and Evie who provided me with a constant source of distraction, both when I needed it and when I didn't.

- *Simon*

Proponents of chaos theory would have us believe that the flapping of a butterfly's wings in a setting distant in time and place can trigger a hurricane. So too does research go. To try to thank by name the efforts of everyone who in some small way contributed to this work would be futile. I would therefore like to thank Professor Stephen Leveson for his endless support and assistance, Dr Thozhukat Sathyapalan, Mr William Ainslie and Professor Ian Morris for their continual guidance and Mr Glenn Miller, Mr Wingzou Wong, Mr Matthew Giles, Mr Peter Sedman, Mr Prashant Jain and Mr Elnazeer Salim for providing me with a pool of patients from which to recruit. Thanks too go to Mr David Locker and Mr Andy Carlisle for their invaluable help with my recruitment efforts, Drs Deborah Phillips and Christine Davey for their help with the study design, Drs Victoria Allgar and Felix Smith for their statistical support and, of course, all the butterflies...

Author's Declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

Chapter 1: Obesity – An Overview

Definition

Overweight and obesity are defined by the World Health Organisation (WHO) as the abnormal or excessive accumulation of fat that presents a risk to health.(1) Although several definitions exist the most widely accepted classification system is that of the WHO which defines obesity on a population level according to the body mass index (BMI), calculated using the following formula:(1)

$$\text{BMI } (kg/m^2) = \frac{\text{Weight in kilograms}}{(\text{Height in metres})^2}$$

When searching for references using the BMI in the older medical literature it should be noted that until it was renamed in 1972 by Ancel Keys the BMI was originally termed the *Quetelet* Index after its discoverer, Belgian mathematician Adolphe Quetelet.(2, 3) Additionally, although the metric units are more commonly employed, older papers may use the following formula which utilises imperial units:(4)

$$\text{BMI} = \frac{\text{Weight in pounds}}{\text{Height in inches}^2} \times 703$$

Although the specific cut-off points used in the WHO classification are arbitrary, a BMI greater than or equal to 25 is considered to be overweight whereas a BMI greater than or equal to 30 is considered to be obese.(1) A BMI greater than or equal to 40 is termed grade 3 or, more commonly, morbid obesity.(4-6) These cut off points have been agreed upon following large scale epidemiological studies which have demonstrated a j-shaped BMI versus all-cause mortality curve.(7, 8) This curve shows an increase in all-cause mortality for overweight and obese individuals as compared to normal weight individuals, beginning at a BMI of 25 and increasing as BMI increases.(7, 8) This increased all-cause mortality is felt to be largely due to vascular disease.(7, 8) The increased all-cause mortality for underweight individuals as compared to normal weight individuals, implicit in the j-shape of the curve, is felt to be related to smoking however it is yet to be satisfactorily explained.(8)

The definition of obesity according to BMI is primarily used for its convenience and accuracy on a population basis as well as its established association with all-cause mortality. However, BMI and body fat percentage (BF%) can vary according to musculature, age, gender and race:

- Mendez and Keys showed in 1960 that the density of skeletal muscle is roughly 1.06kg/l.(9) The density of adipose tissue however has been shown to be around 18% less (0.9kg/l).(10, 11) Therefore the more muscular an individual is the less precise their BMI will become in terms of accurately reflecting their BF%.(9, 10) It is for this reason that defining overweight and obesity on the basis of BMI alone is felt to be particularly inaccurate for athletic individuals whose BMIs are in the intermediate range.(12, 13)
- Associated with the concerns over the accuracy of the BMI classification in relation to muscularity, there is also the issue that with aging there is generally an increase in total body adiposity over the adult lifespan which typically occurs concomitantly with a loss of lean body mass and redistribution of the fat mass.(14, 15) Borkan *et al* showed in 1983 that elderly men had reduced musculature of the limbs and increased abdominal subcutaneous and intramuscular fat compared to middle-aged men.(16) These phenomena mean that an individual's BMI could be potentially stable despite significant increases in total body adiposity.(15, 17)
- The WHO classification also does not discriminate for gender. Males tend to be taller and heavier with a greater lean body mass than females.(18) These differences are present from birth but become more pronounced during puberty then subsequently less dramatic with middle and old age.(19) In 2002 Jackson *et al* showed that for a given BMI the percentage body fat as measured using hydrostatic weighing was 10.4% higher in females than males - these figures are consistent with the existing literature and are reflected in several body-fat prediction formulae such as those proposed by Deurenberg *et al* in 1991.(20, 21)
- Ethnicity too has been shown to play a significant part in body fat composition. In 2002 Deurenberg *et al* showed a 3-5% higher BF% among Asian subjects compared to Caucasians with the same BMI.(22) Several body composition analyses have shown similar significant differences between these groups as well as differences within the various Asian sub-

populations such as Asian Indians, Malayans, Chinese and Pacific Islanders.(23, 24) Jackson et al showed a race effect for Afro-Caribbean females compared to Caucasian females though this effect was not detected in males.(21) A recent study of 538 Mexican-Americans showed almost 87% of men and 93% of women classified as normal or overweight using the BMI classification were shown to be obese on body-fat analysis.(25) As a result of these inter-racial differences some scholars have called for race-specific healthy body-fat ranges to be established in order to better guide public health efforts internationally.(14, 23)

For all the reasons outlined above some researchers prefer to assess obesity using other methods. These include techniques such as dual energy x-ray absorptiometry (DEXA) scanning, bioelectrical impedance analysis (BIA), anthropometric/ skinfold thickness measurement, hip/waist ratio, various prediction formulae/ equations, ultrasonography, magnetic resonance imaging (MRI) and hydrostatic weighing. Each of these has their pros and cons and there is no ideal method of assessment:

- DEXA scanning is an imaging technique in which the patient is irradiated with a beam of x-rays of alternating energies.(26) By using 2 levels of energy the different attenuation values of bone and soft tissue can be calculated to allow assessment of body composition.(26) The technique is simple to use with a short scanning time and low radiation dose and has the advantage of being able to produce precise regional measurements of individual body parts rather than global whole-body readings.(27, 28) However, several studies such as those by Provyn *et al* and van der Ploeg *et al* have questioned the accuracy of DEXA scanning finding that it significantly underestimates BF%.(29, 30) Its use is also limited on a worldwide scale due to the need for expensive equipment and specialist expertise.(28)
- BIA is a technique for measuring BF% which involves the application of electrodes and measurement of the electrical resistance between them.(31) This can be used to determine the total body water content which is used as a marker of lean body mass.(31) BIA is quick, portable, cheap, safe and non-invasive.(31) It is, however, severely restricted in its reliability as the human body is not homogenous, it does not have a constant cross sectional area and

the water, electrolyte concentrations and conductivity can all vary considerably.(31)

- Anthropometric assessment techniques include the estimation of body composition using measurements such as the skin-fold thickness over the triceps or superolateral thigh or waist and hip circumference. Although quick, cheap, safe, simple and non-invasive the estimation of BF% using these techniques has been shown to vary substantially according to the skill and experience of the measurer and accuracy of the callipers.(32) Additionally, due to variations in body fat distribution and the natural redistribution of body fat which occurs with aging many have argued that calliper measurements are an insufficiently reliable indicator of BF%.(33) Also, since callipers can only measure subcutaneous fat, variations in the subcutaneous to intra-abdominal fat ratio will result in unreliable BF% estimates.(34-36) Specific to the obese population Gray *et al* showed that these methods are particularly inaccurate due to the difficulties encountered in obtaining sufficiently large callipers.(37)
- Recently it has been suggested that the Body Adiposity Index ((hip circumference ÷ height$^{1.5}$) - 18) may be a more accurate means of estimating BF% without correcting for age or gender however studies have yet to show this to be the case conclusively.(38)
- The most clinically significant anthropometric measurement is the waist to hip ratio. This measurement, defined as the largest abdominal circumference midway between the costal margin and the iliac crest divided by the largest circumference just below the iliac crest, has several advantages to its use: like skinfold thickness measurement it is quick, cheap, safe, simple and non-invasive but it is has the benefit of greater accuracy.(35, 39) Central adiposity, for which the most commonly used and reliable approximation is the waist measurement, may be of particular relevance to the development of obesity related comorbidities.(35, 40, 41) The main limitation for waist to hip ratio is that the site of measurement and the patients' postprandial status, height, position and depth of inspiration may all affect precision.(35, 42, 43) In addition studies such as Lear *et al* and Carroll *et al* have shown differences between ethnic groups when comparing waist measurements to visceral and subcutaneous BF%.(44, 45)

- Prediction formulae have been developed which approximate the BF% of a patient according to age, gender, BMI and/ or specific anthropometric measurements. These however are of limited value due to their reliance on flawed variables such as BMI and anthropometric assessments.(21) They also cannot be relied upon across all ages, races and BMIs - particularly those at the extremes.(21)
- Ultrasound scans (USS) emit and detect a high frequency reflected wave and translate the distances and intensities of the reflected signals into a visual image.(46) Tissues of differing density will show up as differing visual intensities. This can be used to assess the depth and distribution of adipose tissue and has several key advantages – ultrasonography is safe, quick, non-invasive and cost effective.(47-49) Studies such as Pineau *et al* have shown a high degree of correlation between modern portable USS devices and DEXA scans in terms of BF% estimation.(47) It has been suggested that USS may become routinely used in the future assessment of regional adiposity.(47, 49)
- MRI scanning works by applying a strong magnetic field to the body causing all but one or two out of every million hydrogen atoms to line up in the longitudinal axis.(50) A radiofrequency pulse, specific only to hydrogen, is then directed to the field causing these non-lined up hydrogen atoms' protons to absorb the pulse's energy.(50) When the pulse is turned off the hydrogen atoms return to their natural alignment within the magnetic field and release this absorbed energy as photons creating an electromagnetic signal which is converted into a visual signal on a screen.(50, 51) Since different tissues release the radiofrequency pulses' energy at different rates it is possible to differentiate between tissues in the resulting image.(51) MRI is a very precise and accurate form of imaging which does not involve exposure to ionizing radiation however it is expensive to purchase and run the equipment and specialist expertise is required to operate them.(26) They are useful in an academic and research capacity for whole body composition measurements and for the tracking of metabolic activity within contiguous adipose tissue compartments.(52)
- Hydrostatic weighing has long been used as the gold standard technique for estimating body composition.(53-55) Essentially the technique utilizes the Archimedes principle which states that any object, wholly or partially

immersed in a fluid, is buoyed up by a force equal to the weight of the fluid displaced by the object – in other words a floating object will displace its own weight of fluid.(56) Using the following equation the density of the body in question can be calculated:

$$\frac{\text{Density of Body}}{\text{Density of Water}} = \frac{\text{Weight of Body}}{\text{Weight of Body} - \text{Weight of Immersed Body}}$$

From the calculated body density body composition and BF% can be estimated using formulae such as the Brozek formula proposed in 1963.(57) This method has been shown to be reliable and accurate in terms of estimating BF% but it relies on assumptions which are not necessarily applicable in all circumstances.(55, 58) In addition it requires subjects to be weighed whilst completely submerged in water in full exhalation in a hydrostatic weighing tank and so it is of little use in those populations with no access to such equipment or for whom the experience or physiological demands of the test would be too traumatic (children, the elderly, those with learning difficulties etc).(53)

It is clear that no one method is 100% accurate and all are more difficult to perform than the simple measurement of height and weight. As a result the WHO BMI-based classification remains the most widely favoured system for defining and diagnosing obesity and for this reason this method will be employed in this thesis.

The Scale of the Problem

In the United Kingdom the incidence of obesity among the adult population has increased dramatically over the past few years. In 1993 13% of men and 16% of women were classified as obese.(59) By 2004 these figures had increased to 24% for both sexes.(59, 60) Recent estimates suggest that if current trends continue then these figures will reach 60% for the adult male population and 50% for the adult female population by 2050.(59)

This recent dramatic increase in the prevalence of obesity should not be considered to be solely a problem of developed nations. Obesity rates vary between almost 0% in Eritrea and Vietnam to 85% in Nauru.(61) Currently the global prevalence of

obesity stands at upwards of 400 million adults (6% of the population) and whilst the rise in obesity rates in the developed world may be alarming some developing nations have seen levels increase even faster.(62-64) WHO estimates suggest that by 2015 more than 700 million people (10% of the world's population) will be obese.(64)

Perhaps even more alarming than the rate at which obesity is increasing amongst the world's adult population is the rate at which it is affecting more and more of the world's children. Measuring obesity in children is even more problematic than doing so in adults due largely to the lack of an internationally agreed standard definition. In 1994 the International Obesity Task Force (IOTF) was set up to raise awareness of the worldwide increase in the prevalence of obesity and to implement a global strategy for its management and prevention.(65) Resulting from an IOTF workshop on childhood obesity several classification systems were proposed.(65) Perhaps the most widely accepted definition of childhood obesity was proposed in 2000 by Cole *et al* who suggested an age and gender specific BMI-based cut-off system.(66) This system has been adopted by the IOTF and used in numerous subsequent studies such as Svensson *et al* in 2010.(67) Subsequent analyses, however, have suggested that although it has a high specificity (0.95-1.00) the sensitivity is very low in females (0.22-0.25) and a recent systematic review by Reilly *et al* showed no compelling evidence to suggest an advantage to using either this BMI-based system or a waist circumference-based classification over the use of national BMI percentiles for this purpose.(68, 69)

Regardless of which individual classification system is employed there remains little doubt that childhood obesity levels have increased as much as threefold over the past few decades in almost all nations for which data are available, although a few recent studies have suggested that this increase might be showing signs of abating in the USA, UK and Sweden.(70-74) Nonetheless, it is equally well recognized that children who are overweight or obese from an early age are at an increased risk of being overweight or obese as adults with parental obesity, ethnicity and lower educational status having all been identified as potentially associated risk factors.(67, 70, 75-77) A recent systematic review by Reilly *et al* showed that overweight and obesity in childhood and adolescence are associated with adverse health

consequences with regard to premature mortality and physical morbidity in adulthood with hazard ratios ranging between 1.1 and 5.1.(78)

This increase in the prevalence of obesity needs to be considered in conjunction with the economic burden associated with the condition. Owing to the cost of treating the numerous associated comorbidities the overall cost to a country's health service is estimated to be between 0.1 and 2.8% of the total healthcare expenditure.(79, 80) This figure increases to 9.1% if those with a BMI between 25 and 30 are included.(79) In 2010 the estimated cost to the NHS in terms of premature death and sickness attributable to obesity was £3.6 billion.(81) This figure is exclusive of the cost of various commercial diet and weight control programmes.

Aetiology

On a very simple level the pathogenesis of obesity can be considered to be the result of an energy imbalance – if energy absorption exceeds energy expenditure then the excess is stored in fat cells, or adipocytes, which undergo hypertrophy, with or without hyperplasia, in order to accommodate the extra calories thus resulting in an increase in adipocyte mass and weight gain for the individual.(82-84) In reality however the process is considerably more complex and only partly understood. Several theories and hypotheses have been developed to explain the massive increase in obesity levels over the past few decades. Which of the proposed factors is the most responsible or remediable is the subject of keen debate. The majority of factors focus on the social and environmental influences which result in either increased food (energy) consumption or reduced physical activity (energy expenditure).(85, 86) Whilst reduced physical exercise lessons in schools and increased commercially available portion sizes are often cited social factors other, perhaps less immediately obvious, social developments such as increased sleep debt and less variation in ambient temperature have also been proposed as contributory influences.(86, 87)

In addition to the social, cultural and environmental factors several biological mechanisms have been suggested to explain the ongoing obesity epidemic. Viruses have been known to cause some cases of obesity since the 1980s and thus far 5 animal and 3 human viruses have been identified as causing weight gain by inducing triglyceride accumulation and the maturation of preadipocytes.(87-89) Although the

genetics of obesity do not follow simple Mendelian principles it is well recognized that “fatness” does frequently run in families.(90) The identification of specific genes which predispose to obesity has seen slow but definite progress since 2007 when the first locus unequivocally associated with adiposity - a single nucleotide polymorphism in the fat mass and obesity associated (FTO) gene region - was identified.(91-93) Although genetic factors are felt to account for between 40 and 90% of the population variation in BMI genetic risk factors cannot be held solely accountable.(85, 91, 93) The expression of the various genes felt to predispose to obesity have not changed significantly in the past 50 years and so opponents of the genetic predisposition theory would argue that this is evidence to suggest that social and environmental factors are of greater importance.(85) Interestingly there is evidence to suggest that differences exist between primary care physicians (PCPs) and the lay public regarding their beliefs about the root causes of obesity.(94) Ogden *et al* showed that PCPs tended towards more of a socio-behavioural, psychological aetiology for obesity compared to the lay public who preferred a more biological cause.(94) In addition it was found that PCPs tended to offer patients medical solutions if they believed in biological causes and promoted socio-behavioural remedies if they subscribed to the more social/ psychological theories.(94)

In addition to social, environmental, viral and genetic causes several other medical conditions are also known to either result in, or contribute to, weight gain. These include hypothyroidism, adrenal hormone and sex hormone imbalances, hyperinsulinaemia, eating disorders, personality disorders, depression, genetic syndromes such as Prader-Willi syndrome, smoking cessation and iatrogenic causes such as anticonvulsant or tri-cyclic antidepressant use to name but a few.(6, 90) Whilst all of these secondary causes of obesity are recognized as leading to weight gain it should be borne in mind that these conditions represent the vast minority of cases.(90)

As previously stated, on a simple level obesity only develops when energy intake exceeds energy expenditure over a long period of time. It is, however, becoming more and more clear that the aetiology of obesity is dependent on a number of complex interactions between genetics, metabolic and endocrine function and social, cultural and behavioural influences all of which can profoundly affect this energy

balance.(90, 95) It is unlikely that any single unifying theory will be discovered to explain the aetiology of all cases of obesity.(90) Consequently, is it helpful to consider obesity to be not one, but a group of disorders each of which ultimately manifests as the obese phenotype.(95)

Pathophysiology

The adipocyte should be thought of as being an endocrine gland under the influence of a number of hormones and factors which influence its primary function of maintaining energy homeostasis.(96, 97) Adipose tissue performs this function by esterifying free fatty-acids (FFAs) in times of energy abundance, storing them in the form of triglycerides and finally hydrolysing these triglycerides and releasing the FFAs back into the circulation during times of energy debt.(96) If any of the processes involved in influencing adipocyte activity become dysfunctional then significant weight gain or weight loss may result as a consequence of adipose tissue hypertrophy and/ or hyperplasia.(82-84) In addition to its storage function adipose tissue also releases a number of adipokines, which are cell-to-cell signalling proteins involved in such biological processes as angiogenesis, adipogenesis, extracellular matrix dissolution and reformation, insulin resistance, blood pressure control, steroid metabolism, immune response and haemostasis.(97) In this sense adipose tissue can be considered to be the largest endocrine organ in the body.

Adipose tissue consists of several different cell types.(97) Only around one third of the tissue consists of adipocytes with the remainder being made up of preadipocytes, fibroblasts, stromal cells and white blood cells such as macrophages and monocytes.(97, 98) It is worth considering that adipocytes and macrophages are structurally similar and that preadipocytes have been shown to be capable of differentiating into macrophages.(87, 99) This structural similarity has been suggested as evidence to support the viral theory regarding the aetiology of obesity.(87, 88)

Many hormones and transcription factors have been shown to influence the differentiation of preadipocytes into adipocytes of which the two main players are PPARγ and C/EBPα.(97, 100) Similarly the list of adipokines released by adipose tissue also continues to grow. Of these perhaps the most significant would be leptin,

adiponectin, resistin, interleukin 6 (IL-6) and tumour necrosis factor alpha (TNFα).(83, 96, 97) Leptin, adiponectin and resistin are of particular importance in the study of obesity due to their roles in energy homeostasis, glucose metabolism and insulin resistance respectively.(97) Leptin specifically has been the subject of a great deal of research since its discovery in 1994.(97, 101) It has been shown to be a 16kDa, 167 amino-acid protein released in a pulsatile manner following a circadian rhythm in levels proportional to the amount of energy stored in body fat.(102) It is primarily secreted from adipocytes (it is not present in preadipocytes) but is also produced by a variety of other tissues and has been shown to act on receptors in the hypothalamus to mediate satiety and energy conservation.(97, 102, 103) It is felt to be more physiologically important as an indicator of energy deficiency rather than excess.(103) The discoveries that most obese people had higher levels of leptin than non-obese people and that obese people were usually were resistant or tolerant to leptin lead to initial excitement that it might provide the key to the treatment of obesity.(96, 102) This anticipated breakthrough was quickly dispelled however when it was discovered that leptin administration only lead to weight reduction in the very small number of obese patients with congenital leptin deficiency.(96, 102) Other consequences of leptin activity include reduced secretion of the reproductive and thyroid hormones and increased cortisol production which are felt to be part of its energy conservation function.(102)

Health Related Consequences & Prognosis

The adverse health consequences of obesity are many and varied.(6, 104) Almost every system in the body is affected by obesity although the cardiovascular and endocrinological sequelae tend to be given most consideration. Obesity is well documented as being associated with hypertension and type 2 diabetes mellitus (T2DM), both of which are central risk factors for the development of atherosclerotic plaques which can result in ischaemic heart disease (IHD) and cerebrovascular disease – two of the leading causes of death in the developed world.(6, 104-107)

In addition to the cardiometabolic consequences obesity has been linked to respiratory difficulties such as sleep apnoea, hypoventilation syndrome and asthma.(104, 108-110) From a gastroenterological perspective obesity has been shown to predispose to cirrhosis of the liver, liver cancer, gallstone disease and

gastro-oesophageal reflux disease.(6, 104, 111-113) Links have also been established between obesity and various forms of cancer such as breast, uterine, prostatic and colon cancer and evidence is now emerging to suggest that bariatric surgery can reduce cancer risk postoperatively although the mechanism for this benefit remains unclear.(6, 104, 106, 114, 115)

Whilst this list is by no means exhaustive other conditions and health problems which owe at least part of their pathogenesis to obesity include depression, osteoarthritis, infertility, venous thrombo-embolism, hyperlipidaemia, infertility, chronic kidney disease and urinary stress incontinence.(6, 104) Also of interest is the reduction in perceived quality of life (QoL) experienced by obese individuals which has been shown to exist both in children as well as adults.(116-118) Improvements in QoL have been shown to result from weight loss following bariatric surgery however it has also been shown that failure to achieve the desired goals of surgery can have a negative impact.(116, 118, 119)

All of the aforementioned comorbidities associated with obesity lead to it having a considerable impact on the life expectancy of affected individuals. Although the exact degree to which obesity reduces life expectancy is disputed there remains little doubt that obese individuals can expect to live shorter lives than individuals with a normal BMI.(78, 120-122) Attempts to quantify the reduction in life expectancy imposed by obesity have suggested that, at around 7 years for both sexes, it poses as great a risk as smoking.(122) Part of the blame for the anticipated reduction in life expectancy in the developed world has been attributed to the increased prevalence of obesity over the past few decades and the expectation that this will outweigh the beneficial effects of the reduced rate of smoking in the same population.(122-124) In 2011 a meta-analysis by Pontiroli and Morabito suggested that morbidly obese patients undergoing bariatric surgery had a significantly reduced cardiovascular, all-cause and global mortality as compared to controls (Odds Ratio (OR) = 0.58 CI 0.46-0.73, OR = 0.55 CI = 0.49-0.63 and OR = 0.7 CI = 0.59-0.84 respectively).(125)

Management

The management of chronic conditions such as obesity can be considered to involve three phases; primary prevention (decrease the number of new cases), secondary prevention (decrease the severity of established cases) and tertiary prevention (reduce the level of disability associated with the disorder).(95) In the same way that the aetiology of obesity seems to be the simple result of an energy imbalance the treatment of obesity also would also appear at first glance to be obvious; if the problem is physical inactivity then exercise is the answer and if the problem is overconsumption then dietary restriction is the answer. However, as previously discussed, the reality of the situation is considerably more complex, and whilst "diet and exercise" are central to the public health efforts aimed at primary and secondary prevention and both are capable of resulting in clinically significant levels of weight loss, this weight loss is difficult to maintain for a significant number of patients thus their effectiveness as long-term solutions are limited.(126-130) By contrast surgical methods of weight loss have been shown to produce greater degrees of weight loss with more long lasting results than non-surgical treatment options.(126, 127, 131, 132)

Having excluded reversible causes of weight gain such as hypothyroidism the first line of intervention is, in line with the public health measures mentioned above, to assess the dietary habits of the patient.(95) In all cases, except those with pre-existing pregnancy, terminal illness, osteoporosis, anorexia nervosa, cholelithiasis and in breast-feeding women, the first step is to optimize nutrition and restrict calorie intake.(95, 133, 134) Low calorie diets (LCD) and very low calorie diets (VLCD), as well as over the counter meal replacement programmes, can all provide reasonable levels of nutrition and weight loss in the short term but their long term efficacy is less satisfactory due to the difficulties encountered with continued compliance.(95, 129) Low fat diets have not been conclusively shown to produce better results than calorie-restricting diets.(130, 135) Although several macronutrient diets have been advocated, such as the low-carbohydrate Atkins diet, there is currently no evidence to suggest the superiority of any single one of them.(126) The principle determinant of successful weight loss is the adherence to calorie restriction although this is generally felt to be poor.(126)

Although diet alone has been shown to produce more weight loss than exercise alone it has also been shown that exercise is beneficial in helping to maintain the weight loss.(95, 126, 128, 136) In addition exercise has been shown to result in an improvement in cardiovascular fitness and health related quality of life as well as reducing morbidity even when no significant weight loss occurs.(128, 137) For these reasons the second part of the initial management of obesity involves encouraging an increased level of physical activity in the patient however there is still some uncertainty as to which mode, duration or intensity of exercise is most beneficial in terms of health improvement and weight loss.(95, 130, 133, 134, 136, 138)

Various forms of lifestyle modification or behavioural therapy can also be employed at an early stage as an adjunct to the mainstays of "diet and exercise". A Cochrane review of the literature in 2005 by Shaw *et al* suggested that patients receiving cognitive behavioural interventions such as stimulus control and stress management techniques experienced improved weight reduction, especially when combined with "diet and exercise", compared to those who did not.(139) A review by Foster *et al* in 2005 quantified the degree of weight loss achievable through such techniques as being 8-10%.(140) The attendance of patient support groups has also been advocated as a technique to encourage patients to sustain their efforts in weight reduction although the evidence for their effectiveness is felt to be limited.(130, 133, 134, 139)

For those individuals in whom the above measures are either insufficient or unsustainable the next line of treatment would ideally be to include one of the various drugs which have been developed for use as part of a weight management programme such as Sibutramine, Rimonabant or Orlistat.(95, 126, 127, 130) Several systematic reviews, including a meta-analysis published by the Cochrane group in 2004, have showed that these drugs are capable of inducing modest degrees of weight loss (5-10%) as well as producing varying additional clinical benefits such as improved glycaemic control and lipid profiles when used in the short-term.(130, 141-144) In 2008 Neovius and Narwal performed a review of the evidence and concluded that each of the three main drugs could be considered to be cost-effective.(145) In terms of their primary use of inducing weight loss the main disadvantage of this group of drugs is that due to their considerable side effects they

are generally intended for short term use only and the weight lost is usually put back on following discontinuation.(130, 143) For this reason patients may be tempted to continue taking them indefinitely which is inadvisable. Despite initial optimism however, concerns over the safety of these drugs has led to many of them being discontinued with Orlistat being the only one still licensed for use in Europe.

- Sibutramine acts by inhibiting serotonin and norepinephrine reuptake thereby inducing satiety and preventing diet-induced reductions in metabolic rate.(130) Its less serious side effects include insomnia, nausea, dry mouth and constipation.(146) More seriously it has been associated with an increase in blood pressure and heart rate and for this reason it has been discontinued in numerous countries including the UK, USA and Australia.(146, 147)
- Rimonabant reduces food intake by blocking cannabinoid receptors in the central nervous system thus promoting satiety.(130, 148) It also acts peripherally by promoting adiponectin production resulting in an additional beneficial effect on lipid and glucose metabolism.(148) Its commonest adverse effects include nausea, dizziness, diarrhoea and insomnia.(146) Sadly however, reports of psychiatric disturbances, particularly depression, in patients using the drug lead to its licence being withdrawn in 2009.(149)
- Orlistat is a lipase inhibitor and acts by reducing fat absorption in the gastrointestinal tract.(130) Its main side effects are steatorrhoea, faecal urgency and incontinence, altered absorption of concomitant medication and fat-soluble vitamin deficiencies.(146)

The final choice of treatment for obesity is surgery. Surgical intervention for morbid obesity has been shown to be effective in providing long-lasting weight loss as compared to conservative treatment with the gold standard being the Roux-en-Y gastric bypass (RYGBP) which consistently shows excess bodyweight losses of 70-80%.(132, 150) In addition bariatric surgery has been shown to result in improvements or remission of the cardiometabolic complications of obesity. For example, the overall individual risk from heart disease has been shown to reduce following bariatric surgery with an estimated 4 deaths and 16 cardiovascular events being prevented over 10 years for every 100 patients with cardiac disease undergoing surgery, presumably due to the proven improvement in intimal thickness following surgery.(151-153) Additionally, the RYGBP has been shown to prevent new cases

of heart disease occurring in obese patients with the number needed to treat being calculated to be 77.(154) Hypertension, dyslipidaemia and diabetes mellitus (DM) – all of which are risk factors for atherosclerosis - have each been shown to improve significantly following surgery.(131, 155, 156) The resolution of DM can be defined as glycaemia below the diabetic range in the absence of pharmacological or surgical therapy.(157) Using these parameters T2DM resolution rates of between 80-90% have been reported in numerous studies and systematic reviews.(158-162) This improvement in glycaemic control appears to be particularly encouraging in those recently diagnosed with T2DM and those in whom the excess weight loss was greatest.(163, 164) Interestingly, patients with T2DM whose BMIs are below 35kg/m^2, who currently do not qualify for bariatric surgery in the UK, have also been shown to experience significant improvements in glycaemic control postoperatively.(165)

In addition to being clinically effective, bariatric surgery has long been felt to be cost-effective in the long term with the initial cost of surgery being recouped within 2 to 4 years in the majority of early studies.(142, 161, 166-169) The greatest financial benefit is felt to be seen in younger patients, those without obesity-related comorbidities and those with a BMI between 40-50kg/m^2.(170) In the past few years however more pessimistic projections have been published. In 2013 Finkelstein *et al* reported that whilst the time to breakeven may be as much as 10 years there was still an overall financial advantage from the surgery.(170, 171) Similarly Weiner *et al* were unable to show any advantage over their 6 year study period of bariatric surgery as a whole and suggested that instead of focussing on cost future studies concentrate on the benefits of improved health and well-being of the patients concerned.(172) Assessing the economic costs of a disease is always a complex process however and as such it can only be confidently stated that the jury is still out on whether or not bariatric surgery is a cost-saving intervention. The rationale behind the initial economic optimism was thought to occur despite the expense of the initial surgery ($17-26,000 USD (£10,300-15,800 with an exchange rate of £1:$1.65 USD at time of writing)) due to the substantially reduced long-term medication costs of treating the cardiometabolic comorbidities of obesity.(166, 167, 173-176) Ghiassi *et al* reported in 2012 that in their cohort of 106 patients the mean annual cost of treating hypertension reduced from $63.52 USD to $20.50 USD in those for whom their

hypertension underwent complete remission post-RYGBP and $87.41 USD to $36.82 USD in those for whom it did not.(176) For T2DM patients the equivalent figures were $532.06 USD to $64.52 USD and $1036.60 USD to $322.90 USD respectively.(176)

Currently National Institute of Clinical Excellence (NICE) guidelines recommend surgery as a treatment option for patients meeting the following criteria:

1) The patient has a BMI of greater than 40, or greater than 35 with another significant comorbidity that could be improved with weight loss
2) The patient has been receiving or will receive treatment in a specialist obesity clinic
3) All other appropriate non-surgical treatments have been tried but have failed to achieve or maintain clinically beneficial weight loss for at least 6 months
4) The patient is fit enough for general anaesthetic and surgery
5) The patient will commit to long-term multidisciplinary follow up.(177)

Bariatric surgery is also considered to be the first line treatment in patients with a BMI of 50 or more in whom surgery is considered appropriate.(177)
The initial concept for bariatric surgery came in the early 20th century following the chance observation that patients who had had large sections of stomach or small intestine excised lost significant amounts of weight.(178) The first recorded procedure performed with the deliberate intention of inducing weight loss was a small bowel resection performed by Henriksson in Goethenborg, Sweden in 1952.(179, 180) The irreversible nature of this approach limited its acceptance however, the following year in Minnesota, Buchwald and Varco performed the first jejuno-ileal bypass which was to become the first widely accepted bariatric operation.(178, 179) Since then numerous different approaches and operations have been tried, each with differing strengths and weaknesses and varying degrees of success. Essentially there are three main categories of bariatric operation:

1) Restrictive procedures which aim to limit the volume of food, and therefore the calorific intake, that a patient is capable of ingesting,
2) Malabsorptive procedures which aim to limit the calorific absorption from the food ingested by the patient,

3) Mixed procedures which aim to do both.

Examples of purely restrictive procedures include the gastric wrap, the horizontal gastroplasty and the vertical banded gastroplasty, which eventually gave way to the gastric band and the sleeve gastrectomy.(178, 179) Purely malabsorptive procedures include the original jejuno-ileal bypass and the modern biliopancreatic diversion (BPD).(178, 179) The oldest mixed procedure is the RYGBP however recently other mixed procedures have been developed such as the duodenal switch and the digestive adaptation technique.(178, 179)

In addition to the above there are several approaches that are currently under development which aim to induce weight loss by a variety of mechanisms such as neuromodulation and hormonal manipulation.(181, 182) Currently however, the most commonly performed procedures in the UK are the gastric band, the RYGBP and the sleeve gastrectomy.

The gastric band operation is a purely restrictive procedure in which an adjustable silicone band is placed around the upper part of the stomach to create a 15-20ml pouch, thereby limiting the patient to a significantly smaller volume of food.(182, 183) The initial concept was first suggested in 1976 and over the following few years the technique was refined using varying different materials and approaches.(178, 182) Since 1993 it has been performed almost exclusively laparoscopically.(182) It has the advantages of being reversible, having a short operating time and low perioperative complication and negligible mortality rates.(181-183) Additionally it is associated with fewer nutritional deficiencies in the long-term due to the lack of disruption of the gastrointestinal tract.(181-183) Its main complications include erosion of the stomach in up to 5% of patients, slippage of the band (2-4%) and dilatation of the pouch.(182, 183)

The sleeve gastrectomy is another purely restrictive technique in which the fundus and lateral 80% of the gastric body are excised over a 34 French bougie, usually laparoscopically, to leave a smaller, narrow tube-like stomach with an intact pyloric sphincter.(178, 181) Although not reversible it is quick to perform and can be used as a first stage procedure prior to subsequent conversion to a RYGBP or duodenal

switch.(178, 181) The exact mechanism of its effects and the long-term durability and safety of the technique are as yet unknown.(181, 183)

The until recently the most common bariatric procedure in the world was the RYGBP which, owing to an decrease in its relative popularity in the past few years in North America, has been overtaken by the gastric band despite an overall increase in the frequency of both procedures and the opposite trend occurring in Europe.(184) The RYGBP was first introduced in 1967 and, following numerous modifications and refinements, is now considered to be the gold standard bariatric procedure.(182) It is a mixed procedure in which the restrictive element is provided primarily by the formation of a 30ml gastric pouch and the malabsorptive element results from the construction of a 0.8-1.5cm gastrojejunal anastomosis with a 1-1.5m roux limb which prevents the digestive enzymes produced by the liver and pancreas mixing with the stomach contents until much later in the small bowel.(181) Consequently there is a reduced length of ileum in which the digested food can be absorbed resulting in a smaller calorific intake for the patient. Its main advantage over other forms of bariatric surgery are the rapidity and degree of excess bodyweight lost however it also has the longest operative time of the three main operations and greater perioperative complication and mortality rates (0.5-1%) than the gastric band.(181) Anastomotic leaking, small bowel obstruction, marginal ulceration, venous thromboembolism, renal calculi, incisional herniation and dumping syndrome are all recognized complications of the RYGBP.(182, 183) It is also associated with considerable long-term nutritional deficiencies requiring lifelong monitoring and dietary supplementation where encountered.(181, 185)

Success following bariatric surgery can be defined in several ways but the commonest parameter of success generally used is postoperative excess weight loss. Other useful outcomes are the resolution of comorbidities such as T2DM and hypertension, QoL and the rates of short and long-term complications and mortality. When interpreting the outcomes of bariatric surgery the timescale of the analysis can be crucial. For example the RYGBP has been shown to provide more dramatic results in the early postoperative phase than the gastric band and therefore it could be argued that an outcome at 1-year is misleading and not indicative of the long-term comparison between the two procedures.(186)

In terms of comparative effectiveness there have been numerous studies and meta-analyses performed in recent years with a view to answering the question "Which is the best operation?" These have generally shown that of the three most common operations, on which there is the most data, the RYGBP results in the greatest excess weight loss in both the short and long-term compared to both the sleeve gastrectomy and the gastric band.(187-189) It also has the best patient satisfaction rates, highest postoperative QoL scores and lowest levels of long-term complications and weight loss failure.(132, 187, 189) Comparisons of comorbidity resolution have varied considerably from showing little difference between the procedures to significantly better results with the RYGBP.(188-190) It should be noted that the results in the literature vary considerably for each of the various bariatric techniques primarily due to differences in postoperative follow up practices. However, for the reasons discussed above, the RYGBP is the favoured procedure in Europe and consequently it will be the focus of the study in this thesis.

Chapter 2: Methods of Clinical Prediction

Introduction

In many ways much of the art of practicing medicine boils down to playing the percentages and predicting outcomes. For example, when a clinician takes a history from a patient they ask the questions that they think are the *most likely* to provide them with the information they need to make a diagnosis. They might then order the test or tests that they think are the *most likely* to support or refute the various differential diagnoses under consideration. With each new piece of the puzzle some hypotheses will become *more likely* and others *less likely*. At the end of the process the clinician will then conclude what treatment they think is the *most likely* to result in the most favourable outcome for the patient, based on the information they have obtained. This process is essentially an example of Bayesian probability in action. Bayesian probability is a branch of mathematical probability theory that involves the combination of logic, common sense and observational evidence in order to lead one to a conclusion.(191-193) Bayesian methods are based on the idea that unknown quantities, in this case diagnoses or treatment outcomes, have probability distributions.(191, 192) The probability distribution for a specific diagnosis or outcome is an expression of what is already known or believed about that diagnosis or treatment before it is updated with new information – a process known as Bayesian inference.(191, 192) For example, if a person complains of abdominal pain a clinician may consider the probability that the patient has appendicitis to be 0.1 before enquiring whether or not the patient has had a previous appendicectomy. One of advantages of Bayesian models is that they allow the use of common sense and real-world knowledge to eliminate needless complexity by allowing the model creator, in this case the clinician, to utilise only those factors or quantities which would be logical and consistent with the outcome in question.(191) Using the same example the probability of appendicitis is heavily influenced by enquiring about previous appendicectomy but not so by enquiring about the patient's occupation. After inference, the updated probabilities in a Bayesian model reflect the new levels of belief in (or probabilities of) all possible outcomes coded in the model - in other words when the clinician has finished conducting their focused history they are able to produce a list of differential diagnoses to explain their patient's symptoms, hierarchically categorised by their individual likelihoods.(191)

Given that the above process is the underlying principle of clinical practice, and bearing in mind the ever increasing time constraints imposed upon those involved, it is unsurprising that a great deal of work has been done to help clinicians and patients alike in their decision making. This work can be referred to by many names: prediction rules, probability assessments, prediction models, prognostic models, decision rules, risk scores etc. These are all terms used when multiple predictors, such as patient characteristics and investigation results, are combined using various data mining techniques to estimate the probability of a certain outcome either being present (for a diagnosis) or occurring (for a prognosis), or to identify which intervention is most likely to be effective.(194, 195) The term "data mining" can be defined as the process of selecting, exploring and modelling large amounts of data in order to discover unknown patterns or relationships which provide a clear and useful result to the analyst.(196) Put more simply it means discovery via databases.(196)

Ideally, a reliable predictive model would combine both a high sensitivity with a high specificity.(197, 198) In other words it would correctly identify as high a percentage as possible of the patients fated to have the outcome in question thus maximising the true positive proportion (sensitivity) whilst simultaneously correctly excluding as high a percentage as possible of patients who will ultimately be shown not to have the outcome in question thus maximising the true negative proportion (specificity).(199) In Figure 1 therefore sensitivity can be defined as A÷(A+C) and specificity can be defined as D÷(B+D).

		Actual Outcome	
		Positive	Negative
Predicted Outcome	Positive	A (True Positive)	B (False Positive)
	Negative	C (False Negative)	D (True Negative)

Figure 1 - A Tabular Representation of the Predicted Versus Actual Outcomes of a Predictive Model

It should be noted that there is a difference between a good *predictive* factor and a strong *risk* factor.(197) The positive predictive value of a predictive factor refers to its accuracy in terms of the proportion of patients correctly predicted to have the outcome in question.(200) In Figure 1 this would be A÷(A+B). A risk factor can be identified by calculating the relative risk or odds ratio (the probability of an outcome occurring versus the probability that it will not) of an outcome in patients with the factor in question compared to patients without it.(197, 201) If, however, the factor identified or the outcome being used are uncommon then it is of little clinical use as a predictive factor.(197, 200) A good predictive model shows a good fit between the probabilities calculated from the model and the outcomes actually observed (calibration), whilst also accurately discriminating between patients with and without the outcome.(197, 198, 202, 203) By accurate discrimination we mean that it accurately divides the population into appropriate subsets.(204, 205) For example, if all patients with a measured observation of 0.5 or above die within a certain timeframe and all patients with the measured observation below 0.5 survive then the observed factor can be said to be a perfect predictor of survival within that time frame.

Unfortunately, as a general rule sensitivity and specificity are mutually exclusive – as one rises the other falls.(197) Since both are important to the development of predictive models analysis using receiver-operating characteristic (ROC) curves can be performed in situations where a model results in a continuous risk score, or probability estimate, allowing a visualization of the trade-off between the two and an expression of the overall accuracy of the model.(197, 206, 207) As shown in Figure 2, sensitivity (true positive) is plotted on the y-axis and 1-specificity (false positive) is plotted on the x-axis.(197, 207) The closer a plot is to the top left of the graph then the higher the area under the curve is (also called the c-statistic) and the more accurate or useful a predictive factor can be said to be assuming that sensitivity and specificity are of equal importance.(197, 206, 207) Conversely a plot in the 45 degree diagonal (denoting an area under the curve of 50%) indicates a test no more accurate than chance.(197, 206, 207) Where one sets the limits of acceptability is arbitrary and dependent on a number of factors such as the severity of the outcome and the potential negative consequences of the test such as risk to patients and financial cost.(197, 207)

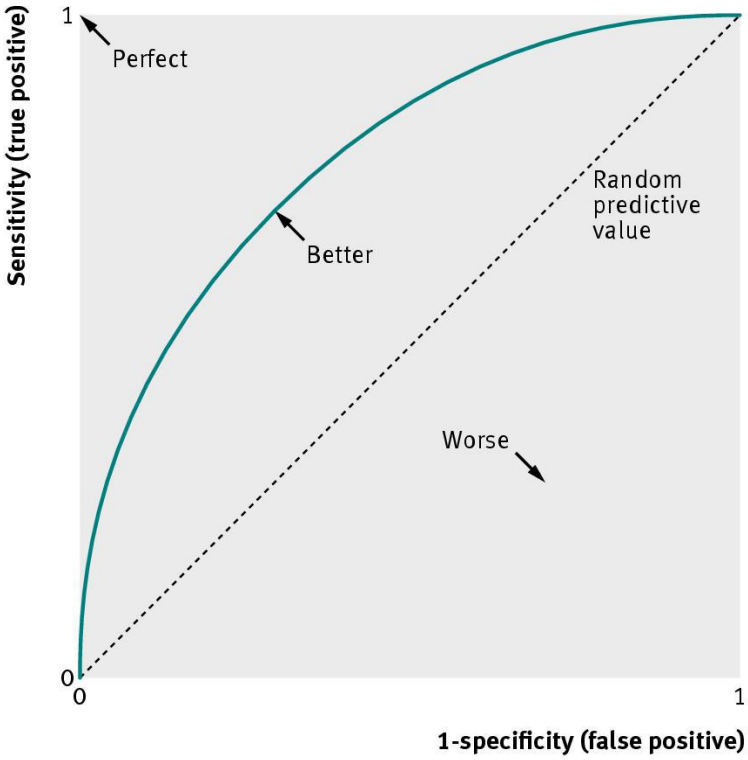

Figure 2 - A Receiver-operating Characteristic (ROC) Curve

Establishing a Clinical Prediction Rule

The transition of a prediction model from abstract concept to general acceptance and adoption follows four distinct phases:

1) Development: the identification of predictors following the analysis of an observational study.
2) Validation: the testing of the rule in a separate population to see if it remains reliable.
3) Impact Analysis: the measurement of the usefulness of the rule in the clinical setting in terms of cost-benefit, patient satisfaction, time/ resource allocation etc.
4) Implementation: widespread acceptance and adoption of the rule in clinical practice.(194, 195, 208-210)

For a prediction rule to gain extensive popularity each of the first three steps needs to be satisfactorily completed before the fourth stage.(194) Establishing the validity of a model which, in layman's terms, is the measure of how much the model predicted what it was meant to predict, is a particularly important step as to accurately predict an outcome in the data set from which the model was derived (internal validation) is no guarantee that the same rule will be anywhere near as accurate in another data set (external validation).(194, 195, 202, 203, 211) Indeed it is well recognized that external validation usually shows a reduction in accuracy compared to the original study typically due to either inadequate development of the model or substantial differences between the derivation and validation populations.(194, 212-214) Since accuracy is fundamental to the subsequent widespread adoption of a rule it is unfortunate that so few predictive models reach the validation stage.(194, 202, 214)

Despite the long-running controversy concerning their usefulness and application the popularity of clinical prediction rules has been shown to be greater now than ever.(194, 215) A simple Medline search performed by Toll *et al* in 2008 using a recommended search strategy developed by Ingui *et al* shows that the number of papers discussing prediction rules has more than doubled in recent years (6,744 papers in 1995 compared to 15,662 in 2005).(194, 216) As discussed above, most of these papers however concern the development of new rules with few articles being published which validate them and almost none confirming their clinical

impact.(194, 202, 210) For example, a recent systematic review of prediction models in reproductive medicine by Leushuis *et al* found that of the 29 models identified only 1 had had its impact on the clinical setting assessed.(202)

Advantages and Disadvantages of Prediction Rules

When appropriately developed and validated, prediction models offer significant inherent advantages as compared to human clinical decision making. Firstly, the statistical models used can accommodate many more factors than the human brain is capable of taking into consideration.(209) Secondly, if given identical data the same result will always be obtained from a statistical model whereas human clinical judgment has been shown to result in both inconsistency and disparity, especially when less experienced clinicians are involved.(208, 209) Finally, and perhaps most significantly, several prediction models have been shown to possess a greater degree of accuracy than that of clinical judgment alone and so one has to wonder why such models are not used more readily in every practice.(208, 209, 215, 217-219)

Liao and Mark proposed in 2003 that the resistance to the widespread adoption of prediction models may reflect tacit acknowledgment that clinicians do not know how to take advantage of such tools.(209, 210) It has been suggested that despite, in some cases, overwhelming evidence to the contrary clinicians may feel that their clinical judgement is at least as accurate as some prediction models and consequently, since they would be inclined to ignore a model's prediction anyway, there is no point in adopting its use.(194, 220) Arguably this might, at least in part, be a result of the relative paucity of validating studies for such rules.(210) Liao and Mark also suggested that such tools may be felt not to be user-friendly in terms of how easily understood they are or the amount of information or computational resources required to perform them and that they may not take into account the continual, dynamic way in which humans gather clinical information.(209, 210, 220) Other potential barriers that have been suggested as to why clinicians may not use prediction models more often include a lack of face validity of the models (the logic behind the model's development does not make sense at face value to the clinician), a lack of familiarity with them and the fear of litigation resulting from utilising such rules over one's own perceived expertise.(194, 210, 221-223) One final reason ventured as to why the implementation of clinical prediction rules is less than one

might imagine is the sheer number of rules available.(209) Where multiple prediction rules exist for the same problem identifying one as clearly superior to another is fraught with difficulty. Not only is it potentially very time consuming but differences in the methodology used in the studies leading to the rules' development may make reliable comparison impossible.(213, 224) Part of the reason for the large number of prediction rules in existence may be due to the wide variety of ways in which such tools can be developed and the fact that no single method of development has been shown to be superior to the others in all aspects.(225)

Types of Prediction Model

Several methods exist for researchers to develop clinical prediction models. Although not an exhaustive list the following techniques can be commonly seen to be used in the literature:

1) Scoring systems derived from univariate analysis -
   Factors are identified on observational studies as being statistically significantly related to the outcome and are subsequently allocated a "score" or "weight". The cumulative final score of all the risk factors present in a patient is used as an indicator of the likelihood of the outcome being present or occurring.(197) Well known examples of this type of prediction model include the Alvarado score for acute appendicitis and the Modified Glasgow score for acute pancreatitis.(226, 227) These models are attractive in their simplicity to devise and use at the bedside but suffer in their accuracy due to the potential inclusion of non-independent risk factors and the arbitrary manner in which factors are weighted.(197)

2) Prediction models based on multivariate analysis –
   These are developed in a similar manner to the above scoring systems except that the analysis of the results from the observational study, which can be done using a variety of multivariate techniques but typically utilises logistic regression, is more refined and therefore less likely to include any non-independent factors.(197) Logistic regression analysis has the added advantage of expressing the relationship between the predictive factors and the outcome in the form of odds ratios which, in addition to being relatively easy to interpret, can also be used to minimise the arbitrary nature in which

factors' weights can be assigned in univariate models.(197) Finally, models utilising logistic regression can often lend themselves well to being represented through a nomogram (see below).(196) Having said all this it is still feasible for independent variables to interact with each other and so the use of multivariate analysis techniques cannot be said to be completely reliable in eliminating this source of bias.(197)

3) Nomograms -

Nomograms are graphical calculating devices, similar to slide-rules, which represent mathematical relationships or laws and allow the user to rapidly calculate complicated formulae to a practical precision as represented in Figure 3.(228) Nomograms may be as simple as the markings on a thermometer or rather more complex such as the Siggaard-Andersen chart used in the diagnosis of acid-base blood disorders.(229) The mathematics and statistics used in the development of a nomogram can be equally simplistic or intricate.(197) Despite the potential complexity involved in their development the advantage of nomograms is that the final prediction tool created is generally comparatively simple to use and in some cases more accurate than other prediction models for the same clinical problem.(197, 230) Other examples of nomograms in common clinical use include those used to predict the likelihood of a patient having prostate cancer from their clinical examination and prostate specific antigen levels and those used to predicted the peak expiratory flow rate of asthmatics based on their age and height.(231, 232)

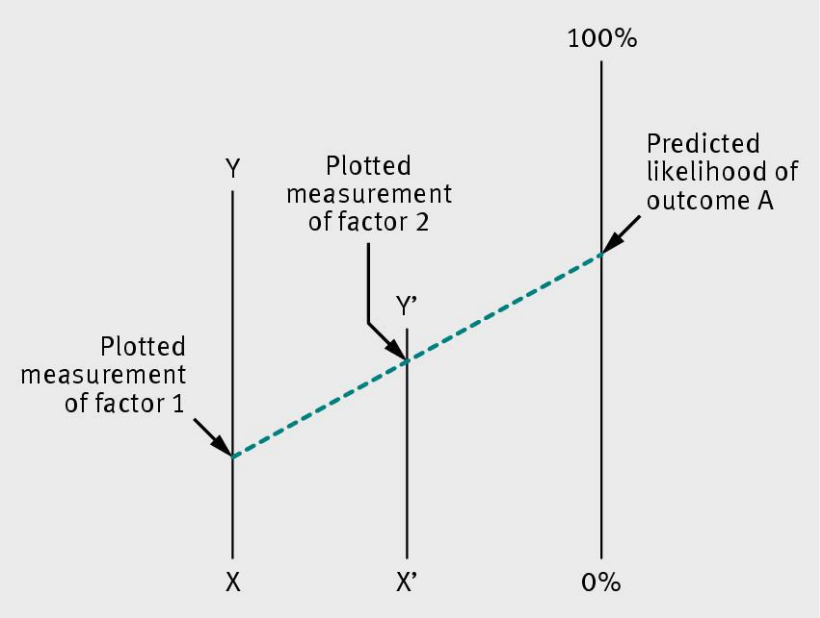

Figure 3 - A Simplified Representation of a Basic Nomogram

4) Prediction utilising artificial neural networks –

Artificial neural networks, often referred to simply as neural networks, are mathematical or computational models based on the operation of biological neural networks.(233) In biology, a nerve cell (or neuron) will receive input from numerous other nerve cells. It will then process all of the input it receives and, if a certain threshold is achieved, either send off an output itself in the form of an action potential or not. Because these nerve cells are all interconnected they are referred to as networks. Artificial neural networks function along similar lines: multiple sources of information (input) are fed into the software programme which interprets it and then produces a dichotomous output. To use Figure 4 as an example, each circle in the first column (the input layer) represents a piece of data which can be put into the neural network programme. The circles in the second column (the hidden layer) represent the neural network programme assigned weight or numerical significance of each piece of data entered into the input layer. The final column (the output layer) represents the dichotomous predicted outcome for the information entered. The main advantage to the use of neural networks is that they have the ability to "learn" mathematical relationships between a series of input variables and the corresponding output.(234-237) This is achieved by inputting a set of data containing both the input data (in the case

of clinical prediction these would be the predictor variables) as well as the outcomes.(234, 235) This is referred to as "training" the neural network. With each new data set the neural network is then able to adjust the internal weights of the various pieces of input data and calculate the probability of a specific outcome.(234) Neural networks offer some distinct advantages over logistic regression models in that they require little formal statistical training to develop and they can implicitly detect complex non-linear relationships between independent and dependent variables as well as all possible interactions between predictor variables.(234, 235) They can also be developed using several different training algorithms.(234) The disadvantages of neural networks are that they have a limited ability to explicitly identify possible causal relationships, they are hard to use at the bedside and they require greater computational resources than other prediction models.(234, 235) They are also prone to "over fitting" in which too many data sets are used in the training of the network causing it to effectively memorise the noise (irrelevant data) in the training set which negatively impacts on its accuracy.(234, 235) A final drawback to neural network use is that the model of neural network development itself is empirical and due to the novelty of the technique there are still methodological issues remaining to be resolved.(234) In a direct comparison between neural networks and logistic regression models Tu *et al* concluded that neural networks had the edge when the goal was outcome prediction but that logistic regression was the preferable technique when trying to look for possible causal relationships between independent and dependent variable or when trying to understand the effect of predictor variables on an outcome.(234)

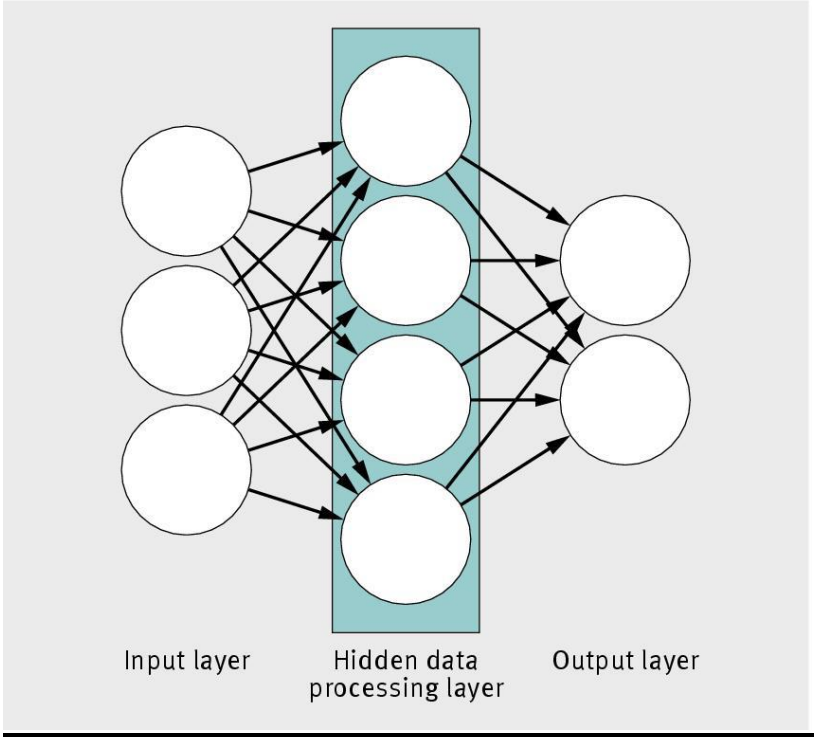

Figure 4 - A Schematic Representation of an Artificial Neural Network (ANN)

5) Decision trees/ Classification and regression tree (CART) analysis – Decision trees or CART analysis uses non-parametric tests to evaluate data and progressively divide it into subgroups based on the predictive independent variables.(197) The variables and discriminatory values used and the order in which the splitting occurs are produced by the underlying mathematical algorithm and are calculated to maximise the resulting predictive accuracy.(197) CART analysis produces "decision trees" which are generally easily understood and consequently translate well into bedside use and everyday clinical practice. To use Figure 5 as an example, each box represents a piece of clinical data with a dichotomous outcome. By following the arrows indicated by the answers to each of the questions in the boxes a clinician will be directed to the predicted outcome for their patient. Examples of CARTs used in clinical practice include those for the prediction of large oesophageal varices in cirrhotics and those used to predict the likelihood of hospitalisation in asthmatics.(238, 239) One drawback of the CART model of prediction is that they have been shown in some cases to be significantly less accurate than other models.(230, 240) This may be due to the "leaves"

on the trees containing too little data to be able to predict outcomes reliably.(196)

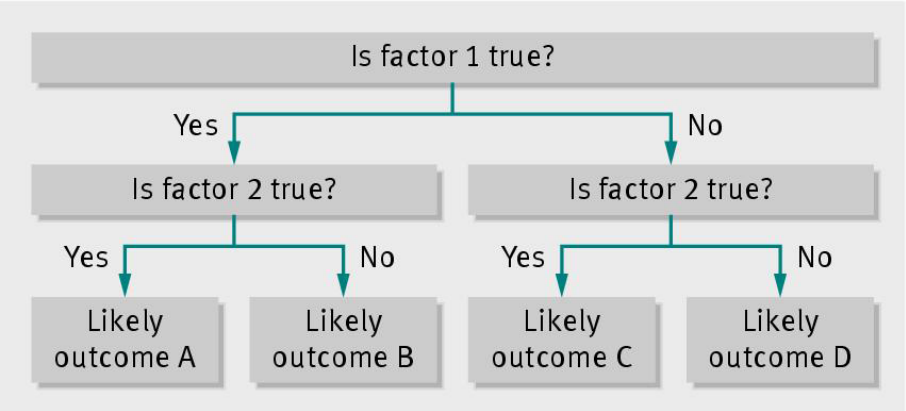

Figure 5 - A Simplified Representation of a Basic Decision Tree

No single model of prediction has been clearly shown to be superior to the others in all applications and each of the five main models discussed above have their pros and cons. In this thesis, however, logistic regression analysis will be utilised to try to achieve the primary outcome of establishing a weighted scoring system to predict the likelihood of successful excess BMI (eBMI) loss and T2DM and/ or hypertension resolution where applicable.

Chapter 3: Preoperative Factors Predictive of Weight Loss – the Current State of Knowledge

Introduction

Bariatric surgery can be defined as having been a success or failure in several different ways. The most obvious and easily measureable parameter of success would be weight loss, which can itself be subcategorised in a variety of ways such as straightforward bodyweight loss, or reduction in BMI or eBMI. In contrast, some clinicians would argue that the resolution of comorbidities is of greater benefit to the patient than the simple loss of weight. Success under these terms should therefore be defined according to validated measures of the various disease states, for example HbA1c reduction to less than 6.5% in patients with T2DM or a systolic BP below 140mmHg in patients with hypertension. Others, however, would argue that functional or psychological improvement should be the goal of bariatric intervention. Then there are the definitions which are harder to apply to the individual such as increased life expectancy or cost-effectiveness. Of course, each of these outcomes can be further sub-categorised according to timescale as it could be argued that improvements in the early postoperative period are of little benefit in the grand scheme of things if they are not maintained in the long term.

There is evidence to suggest that how success is defined following bariatric surgery has a significant impact on results. In 1998 Coleman *et al* showed that by using 4 different commonly used weight-based definitions of success the rates of success varied from 55% to 94% in the same patient group.(241) Findings such as this, in addition to the ongoing debate about how best to define success following bariatric surgery, have resulted in the development of multifactorial outcome scoring systems, the most widely adopted of which is the Bariatric Analysis and Reporting Outcome System (BAROS) initially proposed by Oria and Moorehead in 1998 and subsequently revised in 2009.(242, 243) The BAROS score incorporates analyses of weight loss, changes in co-morbidities and quality of life whilst deducting points for complications and reoperations and has been shown to be a useful tool for measuring bariatric surgery outcomes across differing operations and between differing patient groups.(242, 243)

Why Preoperative Prediction of Success is Important

The vast majority of patients who meet the criteria for having bariatric surgery do not undergo it. The evidence for this lies in the fact that although around a quarter of the UK population is currently classified as obese only 6,500 bariatric operations were performed here in 2010.(59, 60, 244) Of course only some of these 15 million obese individuals will be either morbidly obese or will have the necessary comorbidities required to meet NICE guidelines. Additionally others would be considered to be medically unfit for surgery however this still means that only a small fraction of the obese population who do meet the necessary referral criteria undergo bariatric surgery in the UK each year. Part of the reason for this will be simple logistics – if all eligible patients decided to pursue surgery simultaneously then bariatric services would be overwhelmed due to their finite capacity to provide the service. The other reasons for the comparatively small operative rate in the face of such an apparent demand are, however, less obvious. Evidence detailing why so few patients reach the operating table is lacking although a few studies have been performed looking mainly at the referring practices of PCPs.(245-247) A survey performed by Afonso *et al* in 2010 suggested that a lack of knowledge on the subject of bariatric surgery by both the lay public and PCPs alike may be to blame.(247) It is likely that part of the reason for these groups to be reluctant to pursue a surgical resolution is the fear of complications or mortality, as was suggested by Perlman *et al* in 2007.(246)

Although the health benefits and overall safety of bariatric surgery are well documented it is perhaps not unreasonable to see how a patient or PCP might feel that, in comparison to other operations, surgery for weight reduction is more discretionary. For example, patients thought to have bowel cancer are unlikely to refuse, or be refused, referral to a colorectal surgeon as surgery is generally the safest treatment option and the immediate benefits to the patient are obvious. In contrast, referral of a morbidly obese patient to a bariatric surgeon is more of a last resort to be taken after all conservative attempts at treatment have been tried without lasting success. Even though its effectiveness at providing a long term solution to the problems associated with morbid obesity is well established, and despite its overall safety, there is little point in such a patient undergoing bariatric surgery with all its inherent risks and lifestyle implications if the patient is not going to experience the benefits that are hoped for.

The importance of being able to preoperatively predict a successful result following bariatric surgery is therefore twofold – firstly, it would enable healthcare providers to prioritise those patients most likely to experience a good result thus optimising their resource allocation and, secondly, it would enable clinicians to avoid exposing patients unlikely to benefit from surgery to its inherent dangers. With this in mind it is perhaps unsurprising that a great deal of literature exists on this subject. A recent systematic review by Livhits *et al* searched PubMed® and the Cochrane Database of Reviews and Effectiveness for papers mentioning preoperative BMI and BWL attempts, psychiatric or eating disorders and substance abuse in conjunction with bariatric surgery.(248) 1,007 articles were retrieved following this search of which 115 were eventually included in the review.(248) Given the relatively narrow range of topics studied by Livhits *et al* and the large number of articles they retrieved, and considering the rate at which new papers on the subject are being published, it is not unreasonable to say that to systematically review and meta-analyse every single article on every single factor that had ever been investigated as a potential predictive factor across the whole of bariatric surgery would be a massive, if not impossible, task. Furthermore, since it is well established that the various bariatric operations and techniques give different results, especially when one considers timescale, and that their mechanisms of action are distinct from one another to consider predictive factors across the whole of bariatric surgery, as was done in the Livhits paper, could create a source of bias as it would be rather like looking for reasons why some cars are faster than others without considering variations in engine size. It is for these reasons that this chapter focuses on preoperative factors predictive of BWL following RYGBP only, is touted as being a literature review as opposed to a systematic review and contains no attempt to meta-analyse the factors discussed.

Intraoperative and Postoperative Factors

The purpose of this study is to try to identify which of the established preoperatively identifiable factors are most predictive of a favourable outcome following RYGBP with a view to developing a scoring system which could be applied early on in a patient's preoperative workup to identify those most likely or unlikely to benefit from surgery. Several studies have been performed looking at factors affecting weight loss which can only be established either intraoperatively, such as roux limb

length, or postoperatively, such as attendance at long-term follow up clinics.(249-253) The reason why these factors, although interesting and useful in their own right, are not included in the following literature review is simply that their inclusion in a preoperatively applied tool defeats its purpose as by the time they are known the patient has already had surgery.

Patient Demographic Factors

One of the more contentious issues of recent years has been the ongoing debate about the appropriateness of operating for morbid obesity in the elderly. In 2010 Willkomm *et al* conducted the largest single institution study comparing the outcomes of laparoscopic RYGBP in patients over 65 years of age to those under 65 years of age.(254) Although the operative risk profile was expectedly greater in the older age group the outcomes in terms of complication rates (5% vs 4.3%), mortality (0% vs 0.14%), inpatient stay (1.97 days vs 1.3 days), 30-day readmission rates (6% vs 7.4%) and excess bodyweight loss (eBWL) at 12 (74.8% vs 77.8%) and 24 months (83.4% vs 78.5%) were similar between the two groups.(254) These findings are at odds with those of Flum *et al* (mortality 4.8% vs 1.7% at 30 days, 6.9% vs 2.3% at 90 days, and 11.1% vs 3.9% at 1 year ($p<0.001$)) and Livingston and Langert (OR = 1.04 (95% CI = 1.02-1.07)), who independently concluded that mortality was significantly greater in the over 65 age group and whose papers lead to a reduction in the operative rate among this population.(254-256) The findings and conclusions of Willkomm *et al* do, however, appear to be more in line with those of numerous other single institution studies such as Papasavas *et al*, Hazzan *et al* and Trieu *et al* to name but a few.(254, 257-259) It has been suggested that the discrepancies may be the result of methodological differences in the Flum *et al* and Livingston and Langert studies as compared to the others.(254) Thus far research has concentrated on the effects advanced age has on the safety of RYGBP with little attention being paid to its use as a predictor of weight loss. However, a systematic review published in 2012 by Lynch and Belgaumkar looked at 663 patients in 10 papers and found a mean eBWL of 72.6% at 1 year post-RYGBP with a mortality of 0.3% in patients over 55 years of age.(260) The authors concluded that safety and efficacy of such surgery in this age group was comparable to the general bariatric population and therefore was not a justifiable reason to deny access to treatment.(260)

Several studies have looked at the subject of ethnicity to see whether racial background has an influence on the degree of weight loss following RYGBP though these have tended to focus on the differences between Caucasians and Afro-Caribbeans. Of these studies Harvin *et al* (adjusted odds ratio (AOR) = 7.60 (95% CI =1.83–31.5)), Madan *et al* (eBWL 74% vs 66% (P<0.05)), Anderson *et al* (eBWL 39.8% vs 26.1% (p<0.05)), Kakade *et al* (eBWL 58% vs 73% (p<0.001)), Carlin *et al* (eBWL 67 vs 61% (p = 0.002)) and Buffington and Marema all concluded that Caucasians experience a significantly greater degree of eBWL with only Lufti *et al* revealing a difference between the two groups not reaching statistical significance (eBWL 82.9% vs 60% (p = 0.06)).(261-267) A study in 2008 by Guajardo-Salinas *et al* showed no significant difference between Hispanics and Caucasians which would be in keeping with the findings of an earlier study by Latner *et al* which showed a poorer weight loss outcome in Afro-Caribbeans compared to Hispanics.(268, 269) Why these racial differences exist and whether they exist across all ethnic minorities and all types of bariatric intervention is not currently known. Similarly, the degree to which ethnicity can be used as a prognostic indicator is also currently unquantified but there remains little doubt that certain races do appear to have a more favourable outcome in terms of BW loss following RYGBP than others.

Given that a large proportion of the bariatric surgery in the world is performed in the United States it is perhaps unsurprising that much interest has been shown in the effect of socioeconomic status, specifically medical insurance status, on outcomes following bariatric surgery. The largest of these was the aforementioned database review by Livingston and Langert in 2006 which looked at the data for over 25,000 patients undergoing all types of bariatric surgery.(256) It concluded that Medicare patients tended to be younger and tended to have a greater disease burden than privately insured patients.(256) Most studies looking at insurance/ socioeconomic status in bariatric patients have focused on bariatric surgery as a whole and have used outcome measures such as complication rates, length of stay and mortality.(255, 270, 271) Yuan *et al* published a study in 2009 (also looking at bariatric surgery in general) which, in addition to agreeing that Medicare patients had a greater preoperative disease burden and a significantly higher age-adjusted mortality than non-Medicare patients (2.48% vs 0.76% (p = 0.009)), also showed a reduced eBWL in this group compared to privately insured individuals (60.8% vs 66.5%

($p<0.001$)).(272) Some of the discrepancies may however be due to reduced access to care for Medicare patients as has been shown by Livingston and Burchell and Wallace *et al*.(273, 274) Specific to weight loss following RYGBP there are only a handful of noteworthy papers. The earliest, by Martin *et al* in 1991, found no significant difference in eBWL between the publicly funded group and the privately insured group (66.0±18.4% vs 75.7±23%) but a substantially higher rate of medical (38% vs 13% ($p<0.05$)) and psychiatric complications (23% vs 0% ($p<0.001$)) in the publicly funded group.(275) Interestingly Martin also notes that 45% of the publicly funded patients were able to find employment postoperatively allowing them to reduce their levels of financial support.(275) More recently, in 2008, Alexander *et al* found that when matched for age and BMI the results of RYGBP between the publicly funded and privately funded groups were similar in terms of eBMI loss (64.6% vs 65.2%) as well as average length of stay in days (2.7 vs 2.7).(276) In the same year Melton *et al* published a further study also suggesting that insurance status was not related to suboptimal BW loss following RYGBP ($p = 0.11$).(277)

In addition to insurance status several other socioeconomic factors have also been proposed as having an adverse influence on eBWL following RYGBP. In 2008 Hatoum *et al* found that patients with a lower educational level were likely to lose less weight than those with a college or graduate school qualification ($p = 0.043$).(278) However, the level of knowledge and understanding a patient possesses regarding the nature and mechanisms of bariatric surgery, and how realistic their BWL expectations are, have been shown in separate studies by Orth *et al* and White *et al* respectively not to bear any significance in terms of postoperative BWL.(279, 280) Also, in 2007 Ketchum and Morton found that patients whose jobs required them to work in shifts experienced a lower eBWL following RYGBP at 3 (29.9% vs 43.8% ($p<0.01$)), 6 (46.4% vs 61.3% ($p<0.01$)) and 12 months (56.5% vs 76.8% ($p<0.01$)) as compared to those who worked a traditional 8am to 5pm day.(281)

The usefulness of gender as a predictor of weight loss is questionable since it is an unmodifiable demographic factor rather like age and race. Most studies will mention gender in their results more as an indication of the cohort being investigated however some will provide an analysis of its impact on outcome, such as Ma *et al* who found a slightly greater degree of weight loss in males and Harvin *et al* who found no

significant difference.(262, 282) Again, like age and race, since no meta-analyses have yet been performed to quantify the effect of gender on the degree of BW loss following RYGBP its usefulness as a prognostic indicator is debatable. Nguyen *et al* have suggested that a greater overall mortality for bariatric surgery exists in males (AOR = 1.7) but this figure is derived across all types of bariatric intervention and is not specific to RYGBP.(283)

The analysis of socioeconomic factors published by Lufti *et al* in 2006 found one other demographic factor of significance which, interestingly, does not appear in many other papers – marital status.(263) Whether or not marital status should be viewed as a modifiable factor is open to debate but the discovery that unmarried patients achieved a higher degree of eBWL after laparoscopic RYGBP as compared to their married counterparts (89.8% vs 77.7%; $p = 0.04$) is still worthy of consideration.(263) This finding has subsequently been reported in a study by Livhits *et al* in 2010 who showed an OR of 3.2 ($p = 0.03$) for ≥50% eBWL in single or divorced patients compared to married ones following laparoscopic RYGBP.(251)

Group	Factor	Influence on eBWL	Based on Meta-analysis
Patient Demographics	Age	Comparable	Yes
	Race	Caucasians = Hispanics, Both > Afro-Caribbeans	No
	Socioeconomic Status	No difference between public or privately funded -ve correlation with less education and shift work	No
	Gender	Slightly greater in males to no difference	No
	Marital Status	Greater in single/ divorced	No

Figure 6 - Summary of the Influences of Patient Demographic Factors on eBWL Following RYGBP

Eating-related Behavioural Factors

In terms of the effects of preoperative behavioural factors on success rates following bariatric surgery by far the most research has been done looking at eating behaviours. The specific aspect of eating behaviour that has attracted the most attention has been that of binge eating disorder (BED) in which a person experiences episodes of eating an objectively large amount of food in association with a subjective feeling of loss of control.(284, 285) A literature review in 1998 by Hsu *et al* concluded that BED was associated with weight regain and suggested that further study to improve patient selection was necessary.(284) A recent systematic review of the effects of BED on bariatric surgery as a whole by Mercado *et al* found 2 studies reporting a positive

correlation (BED being associated with greater postoperative BW loss), 4 studies reporting a negative correlation and 14 showing no difference.(286) This finding would appear to be consistent with the few papers looking specifically at eBWL following RYGBP in which some, such as Sallet *et al*, have shown a negative correlation and others such as Alger-Mayer *et al* and Bocchieri-Ricciardi *et al* have shown no difference.(287-289) A meta-analysis of the 4 studies meeting Mercado's criteria for being high quality, however, indicated a positive correlation between BED and eBWL at 12-18 months (mean effect 5.88% eBWL ($p = 0.004$)).(286) No meta-analyses looking specifically at the effects of BED on eBWL following RYGBP are currently available. Interestingly, although at odds with the findings of Mercado *et al* (in that it assumes a negative correlation between BED and post-bariatric surgery BW loss), a recent study by Ashton *et al* suggested that a preoperative BED intervention programme can have a beneficial effect on eBWL in those who respond compared to non-responders (eBWL 68% vs 54% at 1 year ($p<0.05$)).(285) This echoes a similar study in 2008 by Sarwer *et al* who also advocated the wider implementation of preoperative dietary counselling.(290)

A less commonly studied aspect of eating behaviour is that of snacking, or grazing. Part of the reason for this may lie in the fact that there is no universally accepted definition of exactly what "snacking" is which, as was shown in a recent paper by Gregori *et al*, has implications with regard to determining the influence such behaviour has on the development, and presumably treatment, of obesity.(291, 292) Two separate studies, Leite Faria *et al* in 2009 and Kofman *et al* in 2010, have shown that snacking behaviour *postoperatively* was associated with reduced weight loss and weight regain respectively but studies determining the effects of preoperative snacking behaviour on postoperative weight loss are lacking.(293, 294)

Other Behavioural Factors

As compared to eating-related behavioural factors there is a relative dearth of data concerning the effects of other preoperative behavioural influences on postoperative eBWL following RYGBP. Although several studies exist demonstrating the positive influence bariatric surgery has on postoperative physical activity levels and vice versa few studies have attempted to clarify the relationship between preoperative physical activity levels and the degree of weight loss following surgery.(251, 295)

Notable exceptions to this would be Hatoum *et al*, who found that a reduced level of physical activity was the second strongest predictor of decreased eBWL following RYGB after a higher initial BMI ($p<0.001$), and Livhits *et al* who found that a low, medium or high level of physical activity according to the International Physical Activity Questionnaire accurately predicted whether or not a patient was liable to lose less than or more than 50% of their eBMI (OR=3.5 ($p<0.01$)).(251, 278)

In the same way that several papers exist demonstrating the influence of postoperative exercise on eBWL but few exist concerning that of preoperative exercise there are also surprisingly few studies looking at the influence of preoperative outpatient appointment compliance as opposed to postoperative clinic attendance. The only exception to this observation would be the study by El Chaar *et al* published in 2011 who found that whilst gastric band patients who missed more than a quarter of their preoperative clinic appointments had a significantly lower postoperative eBWL at 1 year postoperatively than those who missed fewer than 25% (24.8% vs 33.8%, $p = 0.02$) the same was not true for RYGBP patients (60.1% vs 63.2%, $p = 0.28$).(296)

Although the precise mechanism remains unclear, the relationship between smoking cessation and weight gain is well established.(297) The health benefits of smoking cessation, however, have been shown to far outweigh the detrimental effects of that weight gain which, according to a study by Levine *et al* in 2001, tends to be less than 6kg and is rarely excessive.(298-300) Additionally, since smoking is also known to be a risk factor for post-surgical morbidity and mortality in general, and stopping smoking, even shortly before surgery, has been shown to improve operative safety, bariatric patients who are current smokers tend to be advised to stop prior to their operation.(298, 301-303) Perhaps not unreasonably therefore, most studies looking at the effects of preoperative smoking behaviour in bariatric patients have concentrated on its effects in terms of safety rather than its effects on eBWL. Some studies, such as Dixon *et al*, have found a modestly beneficial effect of smoking in terms of postoperative eBWL whereas others, such as Latner *et al*, have found the opposite.(269, 298, 304) Consequently, the influence of preoperative smoking behaviour on postoperative eBWL following bariatric surgery in general, and RYGBP specifically, remains both unquantified and intriguing in equal measure. As

with preoperative activity levels and clinic attendance the relative lack of data regarding the predictive influence of preoperative smoking status on postoperative eBWL makes each of them worthy subjects for future study.

Group	**Factor**	**Influence on eBWL**	**Based on Meta-analysis**
Behavioural	Eating-related	BED: no influence to slight –ve correlation Snacking: insufficient data	No
	Preoperative physical activity	Strong +ve correlation	No
	Preoperative clinic attendance	No effect	No
	Smoking	Variable	No

Figure 7 - Summary of the Influences of Behavioural Factors on eBWL Following RYGBP

Genetic Influences

Several genes have been identified as being associated with the development of obesity and its associated co-morbidities however few studies exist which have sought to clarify their usefulness as prognostic indicators following bariatric surgery. To date the only study looking at specific genes and their influence on the outcomes following RYGBP is Goergen *et al* in 2011.(305) In this study genotypic possession of single nucleotide polymorphisms in the insulin-induced gene 2 (INSIG2) and the melanocortin-4 receptor (MC4R) obesity genes were not found to have any statistically significant association with eBWL or comorbidity resolution post-RYGBP.(305) Potoczna *et al* published data in 2004 looking at the effects of melanocortin-4 receptor gene variants, pro-opiomelanocortin and leptin receptor gene mutations and G-protein polymorphisms on weight loss following gastric

banding but unfortunately their work did not look at those undergoing RYGBP.(306, 307) However, despite the lack of gene studies looking explicitly at post-RYGBP eBWL, a small number of familial studies have been performed suggesting the existence of a genetic influence. Recently Slotman showed that eBWL was significantly higher at one year post-RYGBP in genetically related patients compared to case-matched controls (76±18% vs 62±19% ($p<0.001$)).(308) Also, Gallagher *et al* suggested in 2010 that pairs of genetically related patients are liable to achieve more similar degrees of eBWL following bariatric surgery compared to co-habiting but genetically unrelated couples.(309) They concluded that heredity accounted for 77% of the variability of postoperative eBWL ($p = 0.0005$).(309) To date, the only monozygotic twin study of note found similar eBWL patterns between 2 of the pairs of subjects studied and proposed that environmental, social support and postoperative management factors were the reasons for the differential eBWL seen in the other 2 pairs of subjects.(310)

Preoperative BMI

Several authors have sought to determine whether or not a patient's preoperative BMI and weight loss history have any bearing on their likely outcome following surgery. The largest such series was published by Still *et al* in 2012 who prospectively recruited 2,365 patients due to undergo RYGBP.(311) In accordance to the majority of the literature on this topic they concluded that whilst a higher preoperative BMI is associated with a greater *absolute* BWL, when considered as a *proportion* the percentage eBWL amongst this group tends be worse.(277, 278, 282, 311, 312) Some papers however have found the opposite to be true such as Czupryniak *et al* in 2007.(313) To date no meta-analysis of these studies has been published and consequently the significance of BMI at presentation can only be considered to be based on level 3 evidence at best.(314) The discrepancy between absolute and proportional eBWL has led some authors such as Wood *et al* to argue that percentage eBWL is not an appropriate measure of success in the higher initial BMI group.(315)

Another commonly asked question seems to be does preoperative BWL influence postoperative success? Two systematic reviews have been published attempting to answer this question. The first, Livhits *et al* in 2009 found 5 papers showing a

positive effect of preoperative BWL in terms of postoperative BWL, 2 papers with only an unsustained short term positive effect, 5 with no difference and 1 with a negative effect.(316) Their meta-analysis suggested that patients who had lost weight preoperatively experienced a 5% greater eBWL postoperatively at 1 year than those who did not (95% CI = 2.68-7.32).(316) Although this systematic review looked at bariatric surgery as a whole it is worth noting that 11 of the 13 papers (over 92% of the patients) included in the meta-analysis investigated preoperative BWL in RYGBP patients exclusively.(316) More recently Kadeli *et* al published a similar review looking solely at RYGBP patients.(317) Of the 11 papers included 6 found a beneficial effect to preoperative BWL and 5 found no difference.(317) Interestingly, a study by Jantz *et al* in 2009 suggested that the number of preoperative attempts to lose weight non-surgically was not associated with eBWL at 1 year post-RYGBP (r^2 = 0.011).(318) In addition to this Madan *et al* reported that patients having to wait longer before undergoing RYGBP (and therefore with more opportunity to lose weight) do not experience any postoperative advantage in terms of eBWL.(319) The implication from these findings would be that to delay surgery to allow patients to lose weight preoperatively offers no advantage but that encouraging them to do so anyway does. Regardless of its effect on postoperative BWL it could be argued that preoperative weight reduction should be encouraged for its other effects such as reduced intraoperative bleeding, shorter and easier surgery and fewer postoperative complications although these benefits remain unproven.(320-323)

Comorbidities

As previously discussed T2DM is one of the major co-morbidities associated with obesity. It is well established that BWL, either surgically or non-surgically, can result in a significant reduction in the severity of T2DM and its health consequences. What is less clear is whether or not the presence of T2DM itself impacts on the likelihood of successfully losing weight following bariatric procedures. Several studies have been published which have attempted to address this issue. The largest of these, Carbonell *et al*, investigated 655 obese patients with T2DM who had undergone RYGBP.(324) Their results suggested that patients with T2DM, particularly those requiring insulin, experienced significantly less postoperative eBWL at 1 year than those without (60.8% ± 16.6% vs 67.6% ± 16.7% ($p<0.0001$)).(324) This finding has been echoed in similar studies by Campos *et al*

(OR 3.09 (95% CI 1.35-7.09 (p = 0.007))), Ma *et al* (p = 0.01) and Hatoum *et al* (p = 0.008) however the outcomes of others, for example Perugini *et al*, have failed to reach significance.(278, 282, 325, 326) To date no systematic review or meta-analysis looking at the predictive value of DM status as concerns post-RYGBP eBWL has been published.

Although the exact mechanisms are not clear there is a great deal of evidence suggesting that a history of sexual abuse in childhood is associated with an increased risk of obesity in adulthood.(327-330) It is thought that weight gain through disordered eating is used by the victim to prevent them attaining a perceived state of body attractiveness thus defending themselves against future attacks.(329, 331) Originally it was thought therefore that victims of sexual abuse, particularly those who had not undergone psychological intervention and support, would fare worse following bariatric surgery.(331, 332) Although some studies have suggested that eBWL following RYGBP is significantly different between abused and non-abused patients at 12 months, such as Fujioka *et al* (57.7% vs 66.3% ($p<0.05$)) and Ray *et al* (p = 0.04)), others such as Grilo *et al* and Oppong *et al* have shown differences not reaching significance.(332-335) Interestingly, however, studies with longer follow up periods, most notably Buser *et al* in 2009 (p = 0.06) and the aforementioned paper by Fujioka *et al* (64.4% vs 71% (p = 0.31)), have suggested that any difference seen at 12 months is eradicated by 24 months.(331, 332) Although no systematic reviews or meta-analyses currently exist on this topic the general feeling is now that a history of sexual abuse should not be seen as a deterrent to bariatric intervention.(331, 332)

Evaluating the impact of psychological or psychiatric co-morbidity on RYGBP outcomes presents its own challenges owing to the range of conditions that can be considered, variations in diagnostic criteria, the variety of different tools that are available to assess the same or similar conditions and the fact that those affected by psychiatric illnesses are not infrequently also affected by other co-morbidities which may introduce a degree of bias. Nevertheless there is a wealth of literature looking at this very topic, primarily concerned with depression and personality traits. In 2008 Ashton *et al* reviewed this literature and argued that there was no good evidence to support the statement that preoperative psychological testing could predict postoperative RYGBP outcomes and therefore that the common practise of excluding

patients based on the results of such testing was unjustifiable.(336) This is in line with the conclusions of van Hout *et al* who, in a literature review three years earlier, stated that whilst outcomes tended to be better in certain patient groups than others the literature for potential predictors of success was far from conclusive.(337) Whilst some studies have found that patients with a history of mental illness experience significantly lower eBWL post-RYGBP others have found the opposite. In separate studies Rutledge *et al* and Kinzl *et al* found that patients with multiple psychiatric diagnoses were more likely to experience less eBWL and BW regain after 12 months than those with one or no such mental health problems ($p = 0.047$ and OR=6.4 (95% CI = 1.3-12.4) respectively.(338, 339) Examples of studies finding a favourable outcome for those with psychiatric co-morbidities include Clark *et al* who studied patients who had previously been treated for either substance abuse or psychiatric illness ($p<0.05$ and $p<0.001$ respectively) and Averbukh *et al* who showed a positive correlation between Beck Depression Inventory scores and eBWL at 12 months ($p = 0.027$) .(340, 341) Several studies have also looked at the significance of personality traits in terms of post-RYGBP BWL however, as stated by Ashton and van Hout no consistent patterns have emerged.(336, 337, 339, 342, 343) As with T2DM and sexual abuse, systematic reviews and meta-analyses in this area are lacking and would doubtless be a valuable contribution to our collective understanding of preoperative outcome prediction.

Institutional Factors

It has been speculated that where one undergoes one's RYGBP may impact on one's likely outcome. Masoomi *et al* reviewed the data from the Nationwide Inpatient Sample database from 2006-2008 and found that of the 304,515 patients undergoing all forms of bariatric surgery over this period those being operated on in teaching hospitals tended to be more high risk and were more likely to develop complications but the early mortality in such institutions was significantly lower.(344) This study was similar in design to Livingston's paper in 2009 which looked at the data for the National Inpatient Survey from 2005 and concluded that whether or not an institution had the status of bariatric centre of excellence did not impact on early outcomes however, like Masoomi *et al*, the study design did not address the impact of institutional status on long term outcomes like eBWL.(344, 345) To date the only study to do this was published by Kothari *et al* in 2010.(346) In a review of their

community-based training hospital's data Kothari *et al* concluded that their results compared favourably with the published literature in terms of major complications as well as eBWL (mean = 72.4%) and that teaching hospital status did not guarantee better long-term outcomes.(346) Clearly since this is an isolated study more evidence is required before this conclusion can be confirmed.

Group	**Factor**	**Influence on eBWL**	**Based on Meta-analysis**
Genetics	-	Insufficient data	-
Preoperative Weight Status	Absolute BMI	Variable	No
	Preoperative BWL	+ve correlation*	Yes
Comorbidities	T2DM	Slight –ve correlation	No
	Sexual abuse	-ve correlation at 1 year but no difference at 2 years	No
	Psychiatric illness	No difference	Yes
Institutional	-	No difference	No

Figure 8 - Summary of the Influences of Non-Demographic, Non-Behavioural Factors on eBWL Following RYGBP

* 92% of patients in meta-analysis were RYGBP patients

Summary

Although many factors have been implicated as being potentially predictive of the degree of eBWL that can be expected post RYGBP few are strongly and consistently supported in the literature. In addition several of these factors are irremediable, such as age and gender, making their inclusion as part of a preoperative patient selection process ethically questionable. Problems such as these make developing such a selection screening tool more challenging but not altogether impossible.

Chapter 4: Preoperative Factors Predictive of Diabetes Mellitus Remission – the Current State of Knowledge

Introduction

As previously mentioned one of the main benefits of bariatric surgery is that it has been shown to reduce the severity of T2DM, in some cases inducing remission lasting several years.(162, 347, 348) Indeed the non-medical media has often touted bariatric surgery as a "cure" for T2DM although specialist medical opinion has tended to shy away from using the term arguing that, unlike conditions with more dichotomous disease states, defining a cure for DM is less straightforward.(157) This is because DM is defined by hyperglycaemia which exists on a continuum and may be impacted over a short timeframe by everyday treatments or events.(157) A consensus statement released in 2009 by a panel of expert endocrinologists, though not the official position of the American Diabetic Association, defined remission of type 1 and type 2 DM as glycaemia below the diabetic range in the absence of pharmacological or surgical therapy.(157) Partial remission was defined as sub-diabetic hyperglycaemia (HbA1c < 6.5%, fasting glucose 5.6-6.9mmol/l (or ≥99 and ≤126mg/dl)) of at least 1 year's duration and complete remission was defined as a full return to normal measures of glucose metabolism (normal HbA1c, fasting glucose < 5.6mmol/l) for the same duration.(157) Prolonged remission was considered to be complete remission lasting 5 or more years.(157) In addition to inducing remission in established T2DM evidence from a non-randomised, prospective, controlled study published in 2012 suggested that bariatric surgery as a whole was more effective than non-surgical means at preventing the development of T2DM in obese individuals independently of BMI (adjusted hazard ratio = 0.17, 95% CI 0.13 to 0.21, p < 0.001).(349)

Bariatric Surgery in Patients with Diabetes

Presently 366 million people worldwide are thought to be affected by DM.(350) A large proportion of these people are also obese and therefore eligible for potentially remission inducing bariatric surgery. A meta-analysis by Buchwald *et al* in 2009 looking at bariatric surgery as a whole showed complete remission of T2DM at 2 years follow up in 78.1% of patients and improvement in T2DM in a further 8.5% with eBWL and T2DM remission rates being greatest in the duodenal switch patients, then RYGBP patients and worst in those undergoing gastric banding.(162)

Similar results were reported in a systematic review by Meijer *et al* in 2011 which showed T2DM remission in 83% of RYGBP patients and 62% of gastric band patients at 2-14 years follow up.(348) Although most of the literature on this topic has focused on results over the first few postoperative years those few studies with longer follow up periods have shown that the phenomenon of T2DM remission persists - for example in 1995 Pories *et al* published a landmark case series in which 82.9% of patients with T2DM prior to surgery who had undergone RYGBP had normal glucose homeostasis parameters at 10-14 years.(131, 347, 351, 352) More recently, in 2010, Fobi reported similar rates of long term remission at 10 years.(347) It should be noted however that all of these papers refer to data either published or collected prior to the publication of the revised criteria for DM remission described in the above paragraph. The reason why this may be significant is that Pournaras *et al* presented data in 2011 from a multicentre study in which patients showed only a 34% complete T2DM remission rate at 1 year according to the new criteria (41% for RYGBP, 26% for sleeve gastrectomy and 7% for gastric banding) suggesting that a revision of the expectations post-bariatric surgery may be necessary for patients and clinicians alike.(353)

Given the impressive results in the obese population with T2DM it is perhaps unsurprising that recently attention has been paid to determining whether or not other groups of DM patients would experience similar rates of remission. To date the only study to investigate the effects of RYGBP on obese patients with type 1 DM reported that 4 of the 5 patients with the condition (out of 2,170 in the series) experienced a reduction in insulin requirements at 3-76 months follow up (mean 29 months).(354) Their mean eBWL was 58.9% (range 47.1-82%).(354) Clearly however the numbers involved in this study make it difficult to draw any firm conclusions. In stark contrast however there is increasing evidence to suggest that patients with T2DM with BMIs below the current cut-off point for bariatric surgery as defined by NICE guidelines may benefit more than initially thought. In a double-blinded randomised controlled trial published by Lee *et al* in 2011 60 patients with T2DM whose BMIs ranged between 25 and 34 kg/m^2 were randomised to either RYGBP or sleeve gastrectomy.(355) At 1 year 93% of the RYGBP group and 47% of the sleeve gastrectomy group had achieved remission according to the definition described by the expert panel in 2009.(355) Within the same BMI bracket, and using only

RYGBP patients, Boza *et al* reported T2DM remission rates of 83% and 65% at 12 and 24 months respectively.(356) A review of the literature published by Reis *et al* in 2012 found that improvements in glycaemic control in the BMI<35 group were comparable between the RYGBP and the gastric band and that a range of different bariatric techniques have been shown to result in substantial benefits in terms of T2DM control.(357) However, as stated in the paper, various methodological differences between the studies used make accurate comparison difficult and in some cases the numbers of patients involved are too small for reliable conclusions to be drawn.(357)

Predictors of Remission

- Short-term

  In comparison to studies looking primarily at eBWL there is a relative paucity of studies attempting to identify predictive factors for the remission of T2DM. The best attempt to establish a predictive model for this issue was published by Hayes *et al* in 2011.(358) Hayes *et al* used 13 preoperative parameters (3 categorical/ nominal variables and 10 continuous variables) and used a variety of statistical and data mining techniques to create 6 different mathematical models.(358) These models were able to correctly identify which patients would experience remission of their T2DM at 12 months follow up in 82.7-87.4% of cases.(358) The most accurate model was a decision tree based on DM status (unrecognised, diet controlled, tablet controlled or insulin controlled), fasting glucose levels, HbA1c and whether or not the patient had concomitant hypertension.(358) The two strongest predictors of T2DM resolution were low HbA1c and no requirement for insulin therapy which were used in all 6 of the models and were the only factors used for 3 of them.(358) These two factors alone successfully predicted T2DM remission in 86.6% of cases in 2 of these 3 models.(358) Interestingly Hayes *et al* also found that a lower preoperative BMI was a negative predictor of T2DM resolution which clearly could have important implications for clinicians with regard to patient selection and the indications for surgery.(358)

Another study addressing the issue of prediction of T2DM remission would be Hamza *et al* who, in 2011, reported that the percentage of *post*operative eBWL was the only predictor of T2DM remission influenced by the choice of procedure and that younger age was a predictive factor independent of the type of surgery.(359) Despite shorter follow up for the RYGBP patients compared to the gastric banding patients (13.4 months vs 23 months ($p = 0.001$)) the eBWL and T2DM remission rates were significantly better in the RYGBP group (59.4% vs 48.8% ($p = 0.031$) and 50% vs 24% ($p = 0.034$) respectively).(359) The finding that greater eBWL results in improved T2DM remission rates echoes that of a previous study by Kadera *et al* in 2009 although clearly this finding is of little relevance to those seeking to predict T2DM remission in preoperative patients.(163) Similar findings regarding patient age have been reported by Jurowich *et al* and Lee *et al* in 2012 who both independently proposed that not only did younger age confer an increased chance of T2DM remission but also that having a shorter duration of T2DM was an independent predictor.(360, 361) This too has been supported in other studies such as the aforementioned Kadera *et al* paper (whose remission group had been diagnosed a mean of 7.2 ± 6.8 years preoperatively versus 11.0 ± 6.6 years in the improved group ($p = 0.037$)) and Hall *et al* who found that patients who had been diagnosed as having T2DM more than 10 years prior to surgery had a significantly reduced chance of remission after RYGBP compared to those diagnosed more recently ($p = 0.005$).(163, 362)

Other factors which have been found to be significantly associated with chances of T2DM remission following RYGBP include the nature and level of preoperative T2DM control. In 2010 Maciejewski *et al* reported that out of 284 patients undergoing bariatric surgery (of whom 99% underwent RYGBP) 52% had achieved remission at 1 year.(363) Those most likely to have discontinued their T2DM medication were those who were treated preoperatively with oral hypoglycaemic agents alone, followed by those on insulin alone with those on both forms of treatment being the least likely to be able to discontinue their treatment (66% vs 44% vs 35% respectively).(363) The OR for remission comparing those on oral

medication alone versus those on insulin with or without oral medication was 2.77 ($p<0.001$).(363) Similar findings have been published since by Jurowich *et al*, Lee *et al* and Zeni *et al* all of whom found that patients whose T2DM was tablet controlled preoperatively, as compared to insulin-requiring, stood a greater chance of remission.(360, 361, 364) Furthermore the Kadera *et al* study suggested that not only did insulin requirement *per se* significantly influence the chances of remission versus mere improvement of T2DM control but also that insulin dose significantly differed between the 2 groups (55 ± 45 units/ day vs 97 ± 67 units/ day respectively ($p = 0.003$)).(163) With specific reference to T2DM control it is perhaps noteworthy that although all 6 of the models proposed by Hayes *et al* used preoperative HbA1c in their analyses other studies have found markedly differing results.(358) For example Jurowich *et al* and Lee *et al* both concluded that preoperative HbA1c is a reliable predictor of T2DM remission whereas others, for example Kadera *et al*, have found no such association.(163, 360, 361) Similarly whilst Hall *et al* reported a significant difference in remission rates between those with a preoperative HbA1c > 10% compared to those for whom it was between 6.5% and 7.9% (50% vs 77.3% respectively) the lowest rate of T2DM remission was seen in those patients whose levels fell between these two groups (36.4%).(362) As a substitute to preoperative HbA1c levels Lee *et al* proposed in 2012 that serum C-peptide levels could be useful as a predictive factor for T2DM remission.(365) In a study of 205 patients of whom 147 underwent RYGBP those with C-peptide levels of <3.0 ng/ml had a postoperative T2DM remission rate of 55.3% as compared to 82.0% and 90.3% for those with preoperative C-peptide levels of 3-6 ng/ml and >6 ng/ml respectively ($p<0.001$).(365) Alternatively, it has been proposed that a more predictively accurate measurement would be the homeostatic model of assessment estimated glucose disposition index (HOMA-DI) which is the product of insulin sensitivity and beta cell sensitivity however presently this measurement is not in common use and there is little evidence in the literature to support this suggestion.(366, 367)

- Long-Term

  As discussed in the opening paragraph the term "remission of diabetes" is preferred to the use of the word "cure" as it implies the potential for the re-emergence of abnormal glucose homeostasis in the future. To date there exist only a handful of papers looking at predictive factors for the long-term durability of T2DM remission. In 2010 Chikunguwo *et al* investigated 157 patients whose T2DM had gone into remission at 1 year post-RYGBP and found that prolonged remission (5 years or more) existed in 89 of them (56.9%).(368) Echoing the conclusions of studies looking at short term remission, Chikunguwo *et al* found that durable remission was most likely in those whose T2DM was initially controlled by diet alone, followed by those on oral hypoglycaemic agents alone with those requiring insulin having the lowest chance of prolonged remission (76% vs 66% vs 28% respectively ($p<0.0001$)).(368) Prolonged T2DM remission was also significantly more likely in men than women (80% vs 52.3% ($p = 0.0144$)).(368) Low eBWL, weight regain and older age were weak predictors of remission.(368) In a similar but smaller study using a shorter follow up period DiGiorgi *et al* found comparable results to Chikunguwo *et al* in terms of reduced durability of remission in those patients who experienced less postoperative eBWL ($p = 0.03$) or weight regain ($p = 0.002$).(369) DiGiorgi *et al* also found lower preoperative BMI to be weakly predictive of T2DM recurrence ($p = 0.05$).(369) Most recently Brethauer *et al* followed 217 patients, in whom 162 had undergone RYGBP, for 5 to 9 years (median 6 years) and observed complete and partial remission rates of 24% and 26% respectively with HbA1c improvement without remission in a further 34%.(370) Echoing previous studies shorter duration of T2DM and higher long-term eBWL predicted long-term remission ($p < 0.001$ and $p = 0.006$ respectively) and recurrence of T2DM which occurred in 19% of patients was associated with longer duration of T2DM ($p = 0.03$), less eBWL ($p = 0.02$) and weight regain ($p = 0.015$).(370)

One potential confounding factor, suggested by Deitel in 2009, is common to each of the above studies referring to short and long-term T2DM remission following RYGBP.(371) In each study it was assumed that the patients in the study

populations had T2DM rather than latent autoimmune diabetes of the adult (LADA).(371) LADA is a form of type 1 DM in which there is gradual autoimmune destruction of the pancreatic beta cells over a period of up to 12 years rather than the peripheral insulin resistance characteristic of T2DM.(371, 372) Because of the slow progression of the disease many patients are erroneously diagnosed with T2DM whereas in actuality in 10% of the phenotypically T2DM population over age the age of 35 and 25% of those below it LADA is the true diagnosis.(371, 372) Given its nature and prevalence it could be argued that the findings of any paper not specifically excluding LADA preoperatively cannot be considered to be reliable.

	Positively Associated with T2DM Remission	Negatively Associated with T2DM Remission
Short Term	Mode of T2DM control (diet > tablet > insulin (low dose > high dose))	Lower preoperative BMI
	Good glycaemic control (fasting glucose/ HbA1c)	Concomitant hypertension
	Younger age at surgery	
	Shorter duration since onset of T2DM	
Long Term	Mode of T2DM control (diet > tablet > insulin)	
	Gender (male > female)	

Figure 9 - Table Showing Preoperative Predictors of T2DM Remission Following RYGBP in the Short and Long Terms

Proposed Mechanisms of T2DM Remission Following Bariatric Surgery

Another potential reason why there remains uncertainty as to which patients will experience T2DM remission following bariatric procedures is that the mechanism, or mechanisms, of this phenomenon are not fully understood. Several theories have been proposed to explain why T2DM improves or resolves after such interventions although none are proven, each have their arguments for and against and none necessarily preclude the others, indeed it is entirely plausible that they all play a contributory role.(355, 373)

Weight loss is often considered to be the driving factor behind the return to normoglycaemia in post-bariatric surgery patients with T2DM preoperatively as there is a wealth of literature demonstrating that non-surgical weight loss

interventions have the same effect on glucose homeostasis.(374-377) For example a Cochrane review by Norris *et al* published in 2005 which pooled the data from 22 studies looking into the effects of non-surgical BWL concluded that changes in HbA1c levels generally corresponded with changes in the subjects' weight.(375) Additional evidence for this theory stems from the fact that improvement in T2DM control is known to occur following gastric banding which, unlike other forms of bariatric surgery, involves less alteration of the normal anatomy and hormonal profile of patients.(374, 378) However, weight loss alone cannot explain why numerous studies have shown that euglycaemia and normal insulin levels return within days of surgery, long before any appreciable BWL has occurred.(164, 379, 380) For example Schauer *et al* found that 30% of their T2DM patients were euglycaemic without medication within 3 days of RYGBP and Wickremesekera *et al* found the same to be true within 6 days for 28 out of the 31 preoperatively T2DM subjects investigated.(164, 380)

Reduced food intake has also been proposed as the underlying mechanism behind T2DM remission following bariatric surgery.(379, 381) Like BWL however, on closer scrutiny this theory does not seem to tell the whole story either. Studies such as Kellum *et al* in 1990 have suggested that vertical banded gastroplasty results in a less dramatic effect on glucose metabolism than RYGBP despite there being a comparable restrictive element in both operations.(379, 382) In contrast, Ballantyne *et al* investigated 56 gastric band patients and 61 RYGBP patients in 2006 and found that, although the homeostatic model of assessment estimated insulin resistance (HOMA-IR) was significantly less in the RYGBP group (2.2 vs 2.6), the changes in preoperative to postoperative HOMA-IR were not significantly different between the groups.(383) These changes in HOMA-IR were found to correlate most closely with preoperative HOMA-IR (gastric band r=0.83, RYGBP r=0.97) leading the authors to conclude that caloric restriction plays a significant part in improved insulin resistance following both procedures.(383) On the other hand additional evidence against the caloric restriction theory stems from the observation that patients undergoing BPD do not experience a prolonged period of reduced food intake, as demonstrated by Cornicelli *et al* in 2010, yet do experience sustained improvement in glycaemic control as demonstrated by Scopinaro *et al* who published data in 2005 showing normalisation of serum glucose without medication in 310 out of 312 BPD patients at

10 years follow up.(379, 384-388) Further evidence against this hypothesis came from a direct comparison between RYGBP and BPD by Alexandrides *et al* in 2009 who found that, despite similar BWL rates between the two groups, the rates of resolution of T2DM at 2 years was 89% and 99% respectively suggesting that gastric restriction alone could not be the sole mediator of improved glucose homeostasis following bariatric surgery.(389) However, some authors have counter-argued that it is not necessary for one mechanism to explain both the short-term as well as the long-term improvements in insulin resistance.(377) In 2005 Gumbs *et al* proposed that reduced food intake, coupled with alterations in the levels of various insulin releasing enteric hormones, could explain the short-term effects of bariatric surgery on glycaemic control but that BWL and reduced fat-mass itself was sufficient to explain the sustained effects.(377)

The third explanation for how bariatric surgery induces T2DM remission revolves around the concept that by altering the anatomy of the gastrointestinal tract such operations bring about changes in the hormonal profile of the body with the effect of preventing the development of T2DM. This theory can be further subdivided into 3 broad camps:

1) The foregut hypothesis -
   Initially put forth by Hickey *et al* in 1998 this theory proposes that procedures such as the RYGBP exclude those parts of the gut responsible for producing the hormone that leads to T2DM.(379, 390, 391) In this model the increased insulin resistance characteristic of T2DM is a protective phenomenon to hyperinsulinaemia stemming from an abnormal hormonal signal from the gut.(379, 390) Alternatively it could be that the opposite is true – that people with T2DM overproduce a hormone in the foregut that induces insulin resistance which causes secondary hyperinsulinaemia.(379) Strong evidence for this theory stems from a paper by Rubino *et al* who showed that exclusion of the proximal small intestine in rats resulted in improved glucose tolerance and that subsequent re-establishment of the normal anatomy reversed this effect ($p<0.001$).(392) Since this finding several studies have shown that duodenal exclusion induced either surgically or by the placement of impermeable endoduodenal plastic sleeves in both animals and humans

produces a similar effect on glucose homeostasis sometimes with minimal degrees of BWL.(393-397)

2) The hindgut hypothesis -

Proponents of this theory argue that the improvement in T2DM control seen following bariatric surgery stems from the expedited delivery of ingested food to the lower bowel via an intestinal bypass and that this causes the release of an enteric hormone which acts to optimise glucose regulation.(373, 392) Evidence for this hypothesis stems from the frequent observation that those bariatric procedures in which an intestinal shortcut is created generally result in the highest and most rapid rates of T2DM remission.(353, 355, 373, 384, 386, 389) Opponents however would argue that in some direct comparisons no significant difference has been shown to exist between the techniques.(188) An example of such a comparison would be Parikh *et al* in 2007 who found that at 2 years postoperatively 34% and 18% of gastric band patients still required oral anti-diabetes medications or insulin respectively as compared to 13% and 13% for both RYGBP and BPD ($p>0.05$).(188) The hormone central to the hindgut theory is often thought to be glucagon-like peptide 1 (GLP-1) which is released by the L cells of the ileum in response to the presence of intestinal nutrients and is known to increase insulin secretion and sensitivity, reduce glucagon secretion and increase pancreatic beta-cell numbers by means of a proliferative and anti-apoptotic effect.(392, 398-401) The evidence implicating GLP-1 comes from studies such as LaFerrere *et al* and Korner *et al* which have demonstrated increased post-prandial GLP-1 levels after RYGBP but not after restrictive procedures or comparable BWL following non-surgical techniques.(388, 402-404)

3) The ghrelin hypothesis –

Cummings *et al* provided initial evidence that ghrelin, a hunger-inducing hormone produced from both the cells lining the fundus of the stomach and the epsilon cells of the pancreas, may be involved in the anorexic and anti-diabetic effects of RYGBP.(373, 405-407) They were able to show that the circulating levels of ghrelin in the bloodstream increased in proportion with BWL following dieting thus implicating it in mealtime hunger and appetite

increases following non-surgical weight loss.(373, 405, 406) Since ghrelin is also known to induce hypoinsulinaemia and insulin resistance, both directly as well as indirectly by increasing growth hormone, cortisol and epinephrine release, it is thought that in bypassing the fundus of the stomach from which 90% of the body's ghrelin is secreted, operations such as the RYGBP may induce disturbances in its regulation resulting in improved glycaemic control.(373, 401, 408-410) Among the more recent evidence Samat *et al* showed in 2013 that insulin sensitivity and postprandial ghrelin suppression 1 year post-RYGBP was associated with BWL in 9 subjects with obesity and T2DM ($p = 0.03$).(411)

Although the above represent the main current theories concerning the mechanism, or mechanisms, of improved T2DM control following bariatric surgery additional hypotheses have been put forward most of which concern the changes known to occur to the levels of other insulinotropic hormones and inflammatory markers. For example it has been shown that following RYGBP the insulin-releasing actions of both enteroglucagon and gastroinhibitory peptide are enhanced and that the levels of insulin-like growth factor-1 and the insulin-sensitising hormone adiponectin are increased, whereas those of the satiety inducing hormones leptin and pancreatic polypeptide are decreased.(379, 382, 391, 401, 412-414) In addition RYGBP patients have been shown to develop increased concentrations of muscle insulin receptors postoperatively alongside decreased levels of intramuscular lipids and fatty acyl-coenzyme A molecules (both of which are associated with insulin resistance).(401, 415-417) Although these findings are undeniably interesting their precise significance or the degree of contribution that they may make to the primary hypotheses remain uncertain.

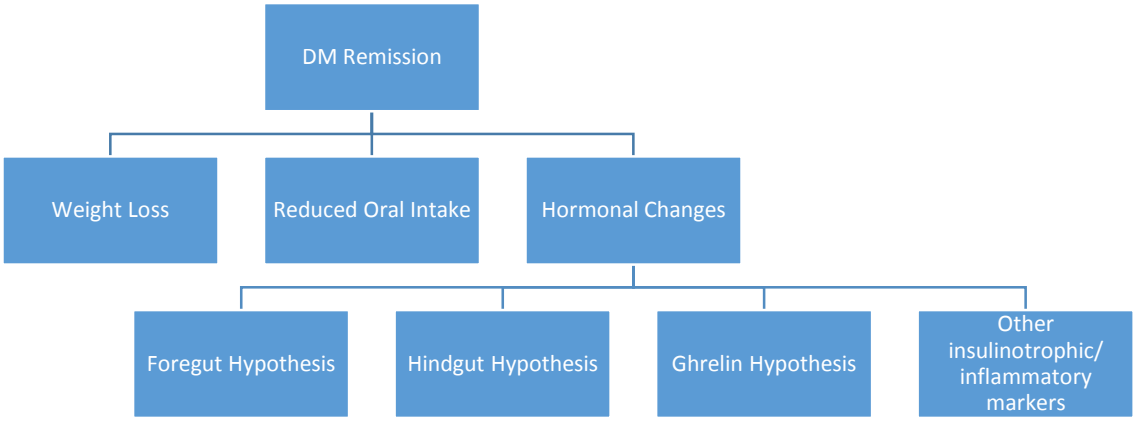

Figure 10 - Proposed Models of T2DM Remission Following Bariatric Surgery

Summary

Whilst it seems to be universally accepted that all forms of surgical and non-surgical BWL improve T2DM, albeit to varying degrees, the exact mechanisms by which they do this remains a source of controversy. There is strong evidence to support the idea that the less severe and short-lived a patient's T2DM is then the greater their chances of achieving a sustained, complete remission following surgery. Whether or not there are any other predictive factors that could be used to identify those individuals most likely to benefit from surgically induced BWL is presently unknown.

Chapter 5: Preoperative Factors Predictive of Hypertension Remission – the Current State of Knowledge

Introduction

The relationship between hypertension and adiposity has been well established in numerous studies over the past few decades across a variety of ethnicities and weight ranges.(418-422) In 1987 Garrison *et al* estimated using data from the Framingham Offspring Study that up to 78% of cases of hypertension in men and 64% of cases in women may be directly attributable to overweight and obesity, concluding that adiposity was therefore one of the major controllable contributors to high BP.(421, 423) The connection between the two has been further clarified by such studies as Jones *et al* who, in 1994, showed that there was a linear relationship between BP and BMI in non-obese Korean subjects – for every BMI increase of 1kg/m^2 in normal weight individuals their diastolic BP rose by 0.89mmHg whereas in overweight individuals their diastolic BP increased by 1mmHg.(420) Subsequently, Doll *et al* found a similar correlation, independent of age and body fat distribution, for 2 distinct populations – one with subjects primarily of African origin in whom hypertension has a high prevalence and the other with subjects primarily of Caucasian origin in whom it is relatively low.(419) In their study Doll *et al* concluded that in the Caucasian group an increase of 1.7 kg/m^2 in BMI, or 4.5cm in waist circumference or 3.4% in waist-to-hip ratio equalled an increase of 1mmHg in systolic BP in men with the corresponding figures being 1.25 kg/m^2, 2.5cm and 1.8% respectively in women.(419) The regression coefficients for age showed a greater effect for these variables on both systolic and diastolic BP in the African group as compared to the Caucasian group suggesting that the increased risk of hypertension in this population is either due to an increased genetic susceptibility or the result of exposure to another unidentified risk factor.(419) Having said all this it is worth remembering that despite the increased prevalence of hypertension in the obese population not all obese patients are hypertensive and not all hypertensive patients have a raised BMI.(418, 424) Although even modest BMI increases and decreases can result in corresponding changes in BP, in both the normal weight and overweight/ obese populations, there is still considerable inter-individual variability.(418, 424-427)

Pathophysiology of Obesity-related Hypertension

Exactly how obesity leads to hypertension is not fully understood however several overlapping theories have been proposed. Central to these theories is the concept that the adipose tissue of overweight or obese individuals is "dysfunctional".(423, 428) This means that the tissue differs from normal adipose tissue by showing increased levels of adipocyte hypertrophy and macrophage infiltration and an altered secretory function of the adipocyte-released hormones (adipokines).(423, 428) It is primarily this altered adipokine secretion component which underpins the hypotheses explaining the aetiology of obesity-associated hypertension.

1) Sympathetic Nervous System Dysfunction

   The main proposed mechanism stems from the proven link between elevated body fat levels and overstimulation of the sympathetic nervous system (SNS).(418, 424, 429-431) Activation of the SNS may induce hypertension by inducing peripheral vasoconstriction, impaired pressure natriuresis and stimulation of the renin-angiotensin-aldosterone system (RAAS).(423) It should be borne in mind however that SNS activity may occur regionally or systemically and much of the literature on this topic is based on the erroneous assumption that systemic markers of SNS activity, such as those of skeletal muscle, are equal in effect to the SNS activity specific to those organs controlling BP, most notably the kidneys.(424, 432, 433) It has been suggested that obesity may not in fact result in systemic SNS hyperactivity but may instead result in a more selective SNS activation process – for example, skeletal muscle and renal SNS activity may be increased in obese patients but cardiac SNS activity may be reduced due to baroreflex inhibition with the increased heart rate seen instead being a consequence of reduced parasympathetic activity.(424, 433-435) Those studies conducted since the development of more site-specific neurochemical and neurophysiological techniques have been pivotal in enhancing our understanding of the pathophysiology of obesity-related hypertension.(432)

   As a result of these site-specific techniques there is now good evidence clarifying the link between body fat levels and SNS activity.(432, 433) Several studies have shown that obese humans demonstrate up to twice the

levels of post-ganglionic muscle SNS activity compared with non-obese subjects.(425, 430, 432, 433, 436-438) It has also been shown that ethnicity plays a role in the relationship between SNS activity, obesity and BP.(423, 439) An example of this finding would be Weyer *et al* in 2000 who found that muscle SNS activity positively related to body fat percentage in Caucasians ($p<0.01$) in whom obesity and hypertension are both widely prevalent but not Pima Indians ($P>0.05$) in whom levels of obesity are high but levels of hypertension are low.(439) In addition studies such as Alvarez *et al* in 2002 have shown that SNS activity is more closely related to levels of intra-abdominal (visceral) fat ($r=0.65$, $p<0.05$) than total fat mass ($r=0.323$, $p<0.05$) or abdominal subcutaneous fat ($r=0.27$, $p = 0.05$) independently of total body fat ($r=0.61$, $p<0.05$). (418, 424, 432, 436, 440) This in turn would explain why such patients have also been found to have a greater association with hypertension and cardiovascular disease.(418, 424, 436, 440) The broad mechanisms linking obesity and SNS activity have been described in several review articles and are briefly outlined below:

- Hyperleptinaemia

  Leptin secretion by adipocytes occurs proportionately to fat mass and its levels are therefore raised in obese subjects.(103, 424, 441) It acts primarily on receptors in the hypothalamus resulting in decreased appetite and increased peripheral thermogenesis. Epidemiological evidence, studies of patients with congenital leptin deficiency and animal studies have also suggested a role for leptin in renal SNS activation and increased BP in the long-term if not acutely.(424, 429, 442-444) It appears to exert its central effects on the SNS by acting on receptors which form parts of other CNS systems such as the melanocortin receptors in the anterior pituitary gland.(424, 445) It is thought that obese subjects may be selectively resistant to the effects of leptin on weight control but not to its influence on renal SNS activity however the exact mechanism for this has yet to be proven.(429, 446)

- Hypoadiponectinaemia

  High molecular weight adiponectin has been shown to have a significant cardio-protective effect in terms of lowering BP and reducing the incidence of atheromatous plaque formation.(424, 447) In contrast to most adipocyte-secreted hormones however its levels in obesity are reduced.(447-449) Exactly how adiponectin reduces BP is not known but studies on rats have shown a dose-dependent reduction in renal SNS function when given either intravenously or intraventricularly.(424, 450) In addition adiponectin has been shown to stimulate the actions of endothelial nitric oxide synthase thus inducing a reduction in vascular tone and smooth muscle proliferation.(423, 447, 451, 452) The elevated levels of free fatty acid and tumour necrosis factor-α seen in obesity are thought to impair nitric oxide synthase function and thus contribute to increased BP in a parallel fashion to the effects of hypoadiponectinaemia.(423, 453)

- Hypoghrelinaemia

  Ghrelin produced in the stomach and pancreas increases during fasting and appears to trigger the sensation of hunger. Rodent studies have suggested that it also counteracts the effects of leptin on melanocortin receptors thus inhibiting renal and systemic SNS activity.(454, 455) Ghrelin has also been shown to increase endothelial nitric oxide production thus resulting in reduced vascular tone.(456) Low ghrelin levels would therefore result in less central sympatho-inhibition and less systemic vasodilatation with a consequential increase in systemic BP.

- Insulin resistance/ hyperinsulinaemia

  Although the evidence implicating insulin resistance in obesity-related hypertension is fairly weak it has been postulated that the two may be indirectly linked by the effects of the former in terms of arterial intimal damage or chronic lipid metabolism dysfunction.(418) The main arguments against hyperinsulinaemia playing a role in hypertension in the acute or subacute settings are that studies of BP in animals in whom insulin has been infused intravenously or directly into the brain do not show a concomitant sustained rise in BP.(418, 424, 457, 458) Equally patients on therapeutic

intravenous insulin drips or with proven insulinomas do not show a tendency towards hypertension.(459, 460)

- Baroreflex dysfunction

  Stretch receptors in the vessel walls of the aortic arch and carotid sinuses respond to beat to beat variations in BP and, via the vagus and glossopharyngeal nerves respectively, send signals to the medulla oblongata which in turn adjusts the autonomic outflow to the heart and blood vessels in order to adjust cardiac output and vascular resistance accordingly to keep BP at a stable baseline.(461) Baroreflex function has been shown to be impaired in obesity, particularly visceral obesity, and there is evidence that this phenomenon is another action attributable to leptin.(434, 440, 462-464) However, since the baroreceptor reflex acts primarily to maintain acute BP stability there remains some doubt as to the degree of influence this mechanism may exert on the BP of obese individuals in the long-term.(418, 424)

- Hypothalamic-pituitary axis (HPA) dysregulation

  In 2000 Bjorntorp *et al* proposed that simultaneous activation of the SNS and HPA may play a role in the development of obesity-related hypertension.(418, 465) Evidence to support this hypothesis followed in 2001 when Grassi *et al* demonstrated that prolonged glucocorticoid administration resulted in SNS inhibition in obese but not normal weight subjects concluding that the HPA may affect SNS function in several ways.(418, 466) Since these early findings it has been suggested that a variety of other metabolites, for example reactive oxygen species, may act on HPA pathways to induce sympatho-excitation with subsequent increases in BP.(467)

2) Renin-Angiotensin-Aldosterone System Dysfunction

   The second major hypothesis linking obesity to hypertension, related to the overstimulation of the SNS, is the concomitant increased activity in obesity of the RAAS which brings about rises in BP via a variety of hormones primarily by directly augmenting renal sodium and water reabsorption and

systemic vascular tone.(423, 468, 469) One of the major RAAS components, angiotensin II, has also been shown to indirectly increase BP acutely through central excitation of the SNS and baroreceptor reflexes.(418, 470) Paradoxically though the effect on SNS function appears to reverse on chronic exposure.(471) Although the RAAS hormones are mainly secreted from organs other than adipose tissue nearly all of them are elevated in obesity and reduce in concentration following BWL.(423, 468, 472-474) For example, Engeli *et al* reported in 2005 that a 5% reduction in bodyweight through dietary restriction by 600 calories per day resulted in reductions of angiotensinogen levels and expression by 27% and 20% respectively and reduction in the concentrations of renin by 43%, aldosterone by 31% and angiotensin-converting-enzyme activity by 12% in adipose tissue (all $p<0.05$) with a concomitant reduction in systolic BP of 7mmHg.(468) It is clear that with the elevated levels of the RAAS hormones in obesity a direct effect on BP could occur however the role of the RAAS on the SNS remains uncertain and is the topic of a great deal of ongoing research.(423)

3) Systemic Inflammation and Oxidative Stress

The third major hypothesis linking hypertension to overweight and obesity centres on the well established association between increased adiposity and elevated levels of systemic inflammation and oxidative stress.(423, 475, 476) It is thought that the common link between the two is that several of the pro-inflammatory cytokines and acute phase reactants have been shown to impair the vasodilatory function of vascular mediators such as nitric oxide.(423, 475, 477) In addition, the direct pressure effect of the adipose tissue on the kidneys is thought to elevate BP by encouraging sodium and water retention.(472, 478) Both pathways would provide plausible explanations as to why visceral obesity is particularly associated with hypertension as patients with predominantly elevated levels of intra-abdominal fat have been shown to have increased levels of systemic inflammatory markers, oxidative stress and intra-abdominal pressure as compared to those with predominantly subcutaneous fat.(476, 479-481)

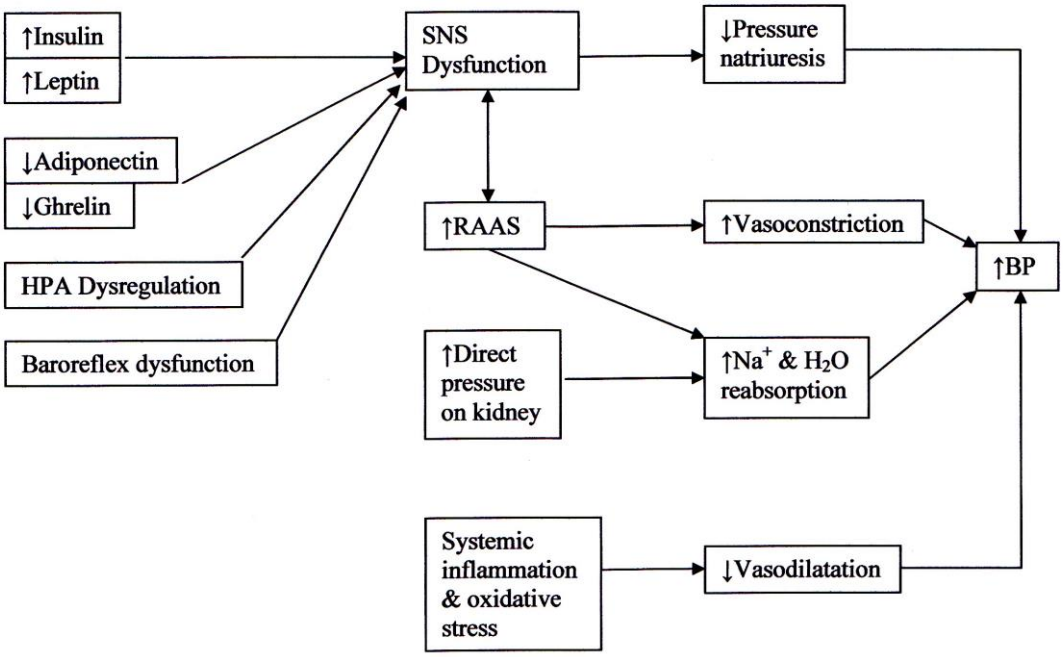

Figure 11 - Mechanisms by which Obesity Induces Hypertension

RYGBP and Hypertension Resolution

In comparison to the number of papers investigating its effects on BMI and T2DM there is a relative dearth of data concerning the influence that RYGBP may have on BP. The largest series of RYGBP on patients with hypertension was reported in 2003 by Sugerman *et al* who investigated 1,025 patients of whom 521 had hypertension (defined as systolic BP ≥150mmHg, diastolic BP ≥90mmHg and/ or the use of antihypertensive medication).(482) At 1-2 years post-RYGBP hypertension had resolved in 69% of these patients (eBWL 66±18%, 91% follow-up rate) with this figure falling to 66% at 5-7 years (eBWL 59±24%, 50% follow-up rate) and 51% at 10-12 years (eBWL 52±25%, 37% follow-up rate).(482) The risk factors for non-resolution of hypertension were increased age, lower eBWL and African-American ethnicity ($p<0.001$, $p<0.001$ and $p<0.02$ respectively).(482) The, perhaps predictable, finding that hypertension is more likely to resolve or improve if more weight is lost echoes those of smaller similar studies such as Carson *et al* who reported 49% resolution and 13% improvement rates at both 12 and 48 months post-RYGBP and Jamal *et al* who reported a 93% resolution rate at 5 years postoperatively.(483, 484) Interestingly Czupryniak *et al* discovered in 2005 that in the majority of post-RYGBP patients not only does BP tend towards normal levels

but also that the natural circadian rhythm of BP is generally restored – a phenomenon which is typically impaired in obesity.(485)

In 2008 Hinojosa *et al* reported a mean eBWL of 66% in a cohort of 95 patients and a 46% complete resolution rate at 12 months post-RYGBP with a further 19% of patients showing some improvement in their hypertension.(486) Analogous to the findings of several studies looking at factors associated with T2DM resolution Hinojosa *et al* found that the duration since diagnosis of hypertension was an independent risk factor for resolution with the complete resolution group having a mean duration of 53 months versus 95 months in the non-resolution group ($p = 0.001$).(486)

The only other published factor associated with successful resolution of hypertension following RYGBP is that of T2DM status. In 2008 Carbonell *et al* reported on a cohort of 3,193 patients of whom 655 (20%) also had T2DM.(324) Although the paper does not state how many of the 3,193 patients had hypertension preoperatively it does conclude that those subjects without concomitant T2DM were significantly more likely to experience resolution of their hypertension than those with both conditions (74.4% vs 63.5%, $p<0.0001$).(324)

Given that there are a variety of mechanisms by which obesity is thought to induce hypertension it is perhaps not unreasonable to think that there may be a variety of mechanisms by which post-bariatric surgery BWL may induce its remission. It used to be thought that BWL itself was the key factor driving the return to normotension however a time-course analysis published by Ahmed *et al* in 2009 showed that improvements in BP occur well before any appreciable BWL.(487, 488) In their cohort of 100 patients systolic and diastolic BPs reduced by 9mmHg and 7mmHg respectively at one week post-RYGBP (both $p<0.05$).(487) These measurements fell by a further 6mmHg and 2mmHg respectively (also both $p<0.05$) with an overall 88% hypertension resolution rate over the remaining 12 month follow-up period suggesting that BWL itself is not the key determinant of BP normalisation following RYGBP.(487) It is likely that the early improvements in BP, if not the long-term improvements, are the result of a hormonal mechanism .(487) One possible explanation was proposed by Sledzinski et al in 2010 who reported a 40% increase in

serum nitric oxide levels 6 months post vertical banded gastroplasty although clearly the differences in the nature of this procedure and the RYGBP make it difficult to draw confident parallels.(489) Improvements in endothelial vasomotor function and aortic elasticity following RYGBP have been described in the literature however the significance of these findings with regard to long term BP control is not clear.(490, 491)

Resolution of Hypertension	
Positive Correlation	Negative Correlation
↓age	↓weight loss Afro-Caribbean ethnicity ↑Duration of hypertension Concomitant DM

Figure 12 - Factors Associated with the Resolution of Hypertension Following RYGBP

Summary

Whilst the link between obesity and hypertension is well established there continues to be some controversy regarding the exact nature of the association. That BWL, whether surgical or non-surgical, effects a change towards normotension appears to be equally well accepted but again the mechanisms by which it does so remain elusive. In comparison to BWL and T2DM remission few attempts appear to have been made to identify factors predictive of hypertension remission. Given the disease burden this would seem to be a worthy area for future research.

Chapter 6: Methods

Rationale and Aims

RYGBP has been shown to be an effective long-term solution for many of the problems associated with morbid obesity.(131, 152, 158, 159) A successful outcome is however highly dependent on the procedure and the patients' postoperative compliance with alterations in their eating habits and levels of physical activity.(277, 335, 337) A great deal of research has been done to try to identify those patients most likely to benefit from surgery in order to optimise resource allocation. Thus far, however, results have been largely inconclusive.(277) The aims of this study are therefore:

1) to assess the impact of a range of factors on the outcome of RYGBP at 1 year postoperatively. The factors to be assessed include:
    a. genetic predisposition to obesity
    b. motivation for seeking surgery
    c. psychological profile
    d. alcohol intake and smoking history
    e. social class and working pattern
    f. cumulative co-morbidity score

2) to utilise this data to suggest a predictive system which can be applied preoperatively to identify those patients who are most likely to lose the greatest amount of their excess bodyweight and, in a subset of patients, to be able to discontinue their medication for T2DM and/ or hypertension.

Hypotheses

No studies have yet attempted to quantify the impact of the factors outlined above in aim 1. Furthermore no widely accepted predictive system currently exists to guide clinicians as to which patients are most likely to benefit the most from RYGBP surgery. It is the assertion of the investigators that in each case the null hypotheses outlined below will be false:

The outcome following RYGBP at 1 year postoperatively will be unaffected by:

a. the patient's genetic predisposition to obesity
b. the patient's primary motivation for seeking bariatric treatment
c. the patient's psychological profile
d. the patient's alcohol intake and smoking history
e. the patient's social class and working pattern
f. the patient's co-morbidities

Consent

In order for any prognostic scoring system to be clinically useful it would need to be applied in the outpatient environment prior to consideration for surgery. For this reason the patients included in this study were assessed and consented at their first clinic appointment. In order to be able to provide informed consent the patients were provided with an information leaflet at the clinic prior to recruitment.

Data Collection

Following consent and recruitment all the patients underwent the routine preoperative workup plus, as part of the study, data was collected relating to factors 3 to 10 as listed below. Appendix 1 shows the data collection sheet onto which all the study data was entered prior to it being transferred to an encrypted spreadsheet. The shaded boxes were filled in at the first preoperative OPD appointment and the remainder were completed using information from the patients' notes.

1) Height measured in stocking feet against a wall mounted metre scale
2) Weights measured using a set of scales
3) Waist, hip and neck measurements measured using a tape measure
4) Genetic predisposition towards obesity as described by Thirlby and Randall (492):
    a. Personal BMI at 10, 20 and 30 years
    b. BMI of parents, siblings and second degree relatives
    c. ethnic group (NB ethnicity is not part of the Thirlby and Randall genetic risk score)
5) Primary and secondary reasons for seeking bariatric surgery
6) Psychological profile as determined by:
    a. Eating behaviour – Three Factor Eating Questionnaire R-18 (TFEQ) (appendix 7) (493, 494)
    b. Physical activity – Baecke Physical Activity Questionnaire (BPAQ) (appendix 8) (495)
    c. Quality of Life – Obese Specific Quality of Life (OSQoL) (appendix 9) (496)
    d. Personality – Ten Item Personality Inventory (TIPI) (appendix 10) (497)
    e. Motivation - University of Rhode Island Change Assessment (URICA) (appendix 11) (498, 499)
7) Weekly alcohol intake and smoking history
8) Social class and work/ shift pattern
9) Drug history
10) Co-morbidities

Equipment required during OPD assessment

Wall mounted metre scale

Bodyweight scales

Tape measure

Definitions used in this study

$$\text{BMI} = \frac{\text{weight in kilograms}}{(\text{height in metres})^2}$$

BMI classifications: $18.5 \geq$ normal weight ≤ 25

$25 >$ overweight ≤ 30

$30 >$ class 1 obese ≤ 35

$35 >$ class 2 obese ≤ 40

>40 morbidly obese

$$\text{Excess BMI (eBMI)} = \text{BMI} - 25$$

$$\text{Excess BW (eBW)} = \text{eBMI} \times \text{height}^2$$

$$\text{Percentage eBMI loss} = 100 - \frac{\text{eBMI postoperatively} \times 100}{\text{eBMI at presentation}}$$

1 year of postoperative follow up was considered to be 250 or more days after surgery. In the event that 2 follow up weights had been recorded in this period the reading closest to 365 days was used.

Whether or not a patient had discontinued their medications for T2DM and/ or hypertension was determined by contacting each individual patient's general practitioner directly at the time of follow up and going through their active and discontinued repeat prescription lists to look for such medications. Provisions to allow this activity had been included in the consent form to avoid any breach of ethics.

Patient Selection

Inclusion criteria:

All patients with Primary Care Trust (PCT) funding referred to York Foundation Trust NHS Hospitals and Hull and East Yorkshire Hospitals NHS Trust for consideration for bariatric treatment and whose baseline investigations did not show a correctable cause for their obesity were approached for inclusion in the study.

Exclusion criteria:

Patients who -

1) Were unable or unwilling to consent to inclusion in the study
2) Were unable or unwilling to undergo the necessary preoperative tests as part of the study
3) Had a correctable cause for their obesity detected at baseline investigation stage

Sample size:

Following consultation with the Trust statistician if was felt that a power calculation was not feasible. It was felt that for each factor being looked at 10 patients would need to be recruited. As the study looked at 13 factors (genetic predisposition, ethnicity, reason for seeking surgery, eating behaviour, physical activity, quality of life, personality, willingness to change behaviour, alcohol intake, smoking history, social class, working pattern and comorbidity) then a minimum of 130 patients would need to still be in the study at 1 year postoperatively. In order to account for dropout then a target of 200 patients to recruit was set. With the annual number of RYGBP cases performed at York Foundation Hospitals NHS Trust and Hull and East Yorkshire Hospitals NHS Trust being approximately150 and 250 respectively at the outset of the study a projected 6 month recruitment period was anticipated.

Data Analysis

Comparability of the patients included in the final analysis as compared to those excluded from it was established by performing the Chi-squared test on the data collected on the 13 factors being investigated. A p value of less than or equal to 0.05 was considered to be significant.

The 13 investigated factors data were then analysed by ANOVA multivariate linear and then binary logistic regression analysis using the software package SPSS (version 22, IBM) to determine whether or not there was a significant association with regard to percent eBMI loss at 1 year post-RYGBP both in isolation and in comparison to the other factors.

Preoperative and postoperative HbA1c and blood pressure measurements recorded in those patients taking medications prior to RYGBP for T2DM and hypertension respectively were analysed for significant differences using a paired t-test. The 13 investigated factors were then analysed using binary logistic regression analysis to identify which factors were significantly associated with medication discontinuation. Each of these tests were performed using the same statistical software package.

In addition the following factors were further analysed according to their component sub-sets by both linear regression and binary logistic regression analyses:

i) Reason for seeking surgery (primary & secondary reasons),
ii) TFEQ (overall, cognitive, uncontrolled, emotional),
iii) BPAQ (overall, work, sport, leisure),
iv) OSQoL (overall, physical, vitality, relations, psychological),
v) TIPI (extravert, agreeable, conscious, emotional stability, openness to experiences),
vi) Cumulative comorbidity (ischaemic heart disease (IHD), hypertension, obstructive sleep apnoea (OSA), chronic obstructive pulmonary disease (COPD), T2DM, polycystic ovary syndrome (PCOS), psychiatric history, previous sexual abuse and other significant comorbidity).

The SPSS syntaxes of the analyses are listed in appendix 13.

Definition of Successful Outcome

For the purposes of this study the primary end point to be used was the percentage reduction in eBMI at 1 year post surgery in relation to eBMI at the first clinic appointment for the linear regression analysis and eBMI loss greater than or equal to 70% for the binary logistic regression analysis. The secondary endpoints were resolution of T2DM and hypertension with cessation of oral hypoglycaemic, insulin or antihypertensive medications also at 1 year post surgery.

Chapter 7: Results

After the commencement of the recruitment phase PCT referral policy changes caused a dramatic reduction in the number of bariatric procedures being done at both study sites. Consequently, as shown in Figure 13, despite lengthening the duration of the recruitment phase by a further six months, only 129 patients could be recruited into the study (i.e. 129 patients provided written, informed consent to participation in the study, completed the interview section, had the necessary preoperative body measurements recorded and completed all of the psychological profile tools in full). Out of these 129 patients, however, only 60 patients had undergone a RYGBP *and* had 12 month postoperative follow up data available thus making their data sets complete and eligible for analysis. This group will henceforth be referred to as the study group (SG). The 69 patients for whom analysis was not feasible (henceforth referred to as the exclusion group (EG)) had either not undergone a RYGBP or did not have 12 month postoperative follow up data.

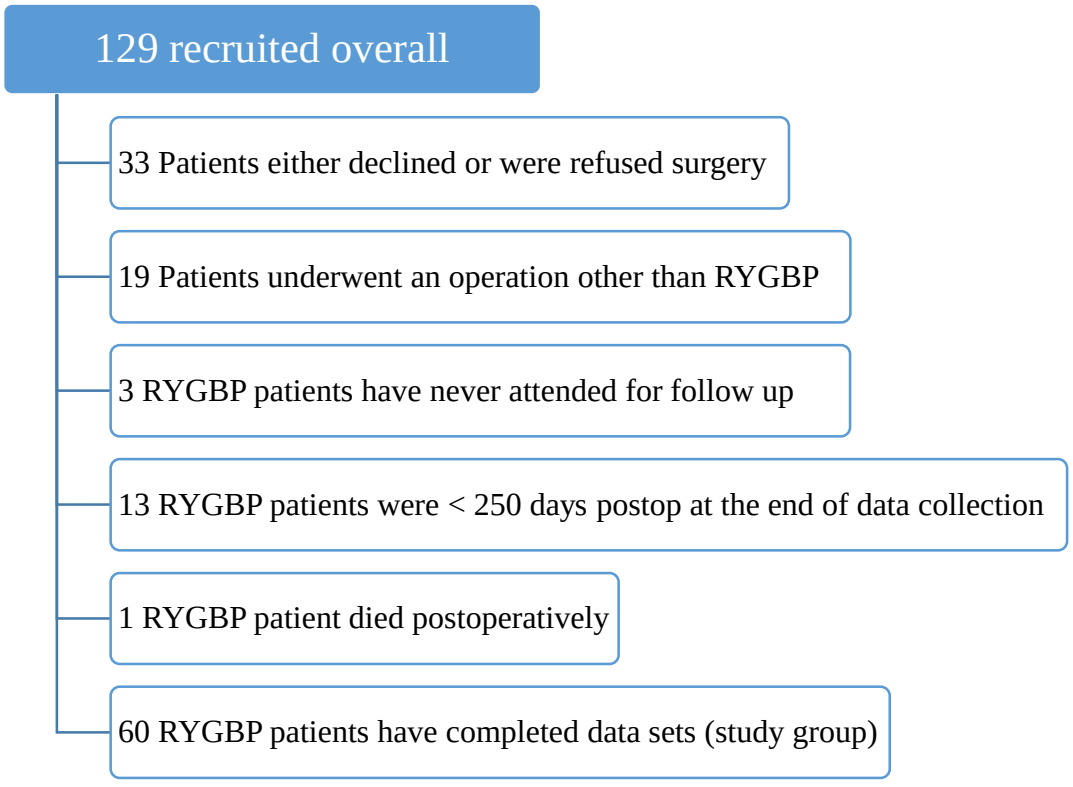

Figure 13 - Illustration Demonstrating the Reasons for and Numbers of Excluded Patients

Analysis of the Generalisability of the Investigated Factors on the Primary Outcome

All 129 recruited patients had completed data sets with regard to the 13 factors being investigated (genetic predisposition, ethnicity, primary reason for seeking surgery, overall scores for the TFEQ, BPAQ, OSQoL, TIPI and URICA , alcohol intake, smoking history, social class, working pattern and cumulative comorbidity). As shown in Figure 14 social class and cumulative comorbidity were significantly different between the SG and EG ($p = 0.03$ and $p = 0.000$ respectively) and therefore could potentially represent confounding factors. The other 11 investigated factors were all comparable between the groups.

Factor	Study Group		Excluded Group		p value
	Min-Max	Mean (SD)	Min-Max	Mean (SD)	
Genetic Risk	0 - 85	38.8 (22.1)	0 - 90	34.0 (24.4)	0.158
Ethnicity	Caucasian 59 Mixed Race 1		Caucasian 66 Mixed Race 1 Asian 2		0.286
Primary Reason for Seeking Surgery	Life Expectancy 7 Quality of Life 20 Comorbidities 30 Appearance 3		Life Expectancy 13 Quality of Life 19 Comorbidities 32 Appearance 4 Other 1		0.66
TFEQ	25 – 55	42.3 (6.8)	25 – 60	42.1 (7.8)	0.100
BPAQ	10 – 60	35.7 (12.2)	9 – 52	30.4 (12.1)	0.141
OSQoL	-486.9 – 1862.3	659.4 (604.9)	-518.7 – 1862.3	881.7 (537.8)	0.484
TIPI	21.0 – 67.0	44.9 (9.2)	22.0 - 63.0	46.1 (8.7)	0.400
URICA	7.3 – 14.0	10.1 (1.3)	6.9 – 14.0	10.4 (1.5)	0.223

Figure 14 - Table Showing Generalisability and Comparison of Investigated Factors Between SG and EG

Social Class	Professional	6	Professional	6	0.030
	Managerial	4	Managerial	7	
	Skilled (non-manual)	7	Skilled (non-manual)	8	
	Skilled (manual)	4	Skilled (manual)	4	
	Partly Skilled	7	Partly Skilled	2	
	Unskilled	12	Unskilled	6	
	Retired	2	Retired	16	
	Unemployed	18	Unemployed	19	
	Student	0	Student	1	

Alcohol Intake	0 – 30	2.1 (5.9)	0 - 30	2.9 (6.6)	0.601
Smoking History	Never	25	Never	32	0.679
	Current	18	Current	16	
	Stopped	17	Stopped	21	
Working Pattern	Non-shifts	31	Non-shifts	26	0.137
	Shift Work	9	Shift Work	8	
	N/A	20	N/A	35	
Cumulative Comorbidity	No comorbidities	6	No comorbidities	5	0.000
	1 Comorbidity	17	1 Comorbidity	10	
	2 Comorbidities	13	2 Comorbidities	20	
	3 Comorbidities	21	3 Comorbidities	9	
	4 Comorbidities	2	4 Comorbidities	11	
	5 Comorbidities	1	5 Comorbidities	5	
			6 Comorbidities	9	

Figure 14 (continued) - Table Showing Generalisability and Comparison of Investigated Factors Between SG and EG

In addition the component sub-sets of the investigated factors were analysed. As shown in Figure 15 the leisure time index of the BPAQ ($p = 0.007$), the vitality component of the OSQoL ($p = 0.002$) and the existence of preoperative hypertension ($p = 0.043$) were all found to be significantly different between the groups.

Factor	Study Group		Excluded Group		p value
	Min-Max	Mean (SD)	Min-Max	Mean (SD)	
Secondary Reason for Seeking Surgery	Life Expectancy 12 Quality of Life 18 Comorbidities 8 Appearance 8 Other 14		Life Expectancy 7 Quality of Life 25 Comorbidities 18 Appearance 5 Other 14		0.171
Cognitive Restraint	6 – 21	14.4 (3.4)	6 – 21	13.9 (3.5)	0.175
Uncontrolled Eating	10 – 33	20.3 (6.0)	9 – 36	20.8 (6.2)	0.383
Emotional Eating	3 – 12	7.9 (2.4)	3 – 12	7.3 (2.9)	0.574
Work Index	0 – 4.4	2.5 (1.3)	0 – 4.5	1.9 (1.4)	0.174
Sport Index	0.75 – 4.5	1.7 (0.7)	0.75 – 3.25	1.6 (0.6)	0.306
Leisure time index	1 – 4.25	2.3 (0.7)	1.0 – 3.75	2.2 (0.7)	0.007
Physical Activity	-250.8 – 803.2	262.3 (283.6)	-220.5 – 803.2	388.3 (266.1)	0.423
Relationships	-107.6 – 179.3	54.6 (80.1)	-107.6 – 179.3	64.4 (76.5)	0.525
Vitality	-165.3 – 563.7	248.0 (226.6)	-66.5 – 563.7	307.3 – 174.4	0.002
Psychological State	-189.7 – 316.1	94.5 (140.4)	-189.7 – 316.1	121.6 (148.1)	0.058

Figure 15 - Table Showing Generalisability and Comparison of Investigated Factor Component Sub-sets Between SG and EG

Factor	Study Group		Excluded Group		p value
	Min-Max	Mean (SD)	Min-Max	Mean (SD)	
Extravert	2 - 14	8.1 (3.0)	2 - 14	8.4 (3.1)	0.850
Agreeableness	2 - 14	10.1 (2.9)	2 - 14	9.9 (2.9)	0.759
Conscientiousness	2 - 14	9.5 (3.3)	2 - 14	9.6 (2.9)	0.929
Emotional Stability	2 - 14	8.0 (3.1)	2 - 14	8.3 (3.3)	0.257
Openness to Experiences	4 - 14	9.2 (2.6)	3 - 14	9.8 (2.7)	0.954
IHD	No 60	Yes 0	No 65	Yes 4	0.123
OSA	No 55	Yes 5	No 55	Yes 14	0.080
COPD/ Asthma	No 49	Yes 11	No 48	Yes 21	0.125
T2DM	No 45	Yes 15	No 43	Yes 26	0.134
Hypertension	No 44	Yes 16	No 38	Yes 31	0.043
PCOS (excluding male patients)	No 41	Yes 4	No 51	Yes 1	0.180
Psychiatric History	No 30	Yes 30	No 30	Yes 39	0.484
Sexual Abuse	No 50	Yes 10	No 63	Yes 6	0.191
Other	No 32	Yes 28	No 29	Yes 40	0.069

Figure 15 (continued) - Table Showing Generalisability and Comparison of Investigated Factor Component Sub-sets Between SG and EG

Comparison of the Study Group with the Exclusion Group

As shown in figures 16-19 there were no significant differences between the SG and the EG at recruitment in terms of gender (p = 1.000), decade of life (p = 0.240) and BMI range (p = 0.339).

Gender	Study Group	Exclusion Group	Total
Female	45	52	97
Male	15	17	32
Total	60	69	129

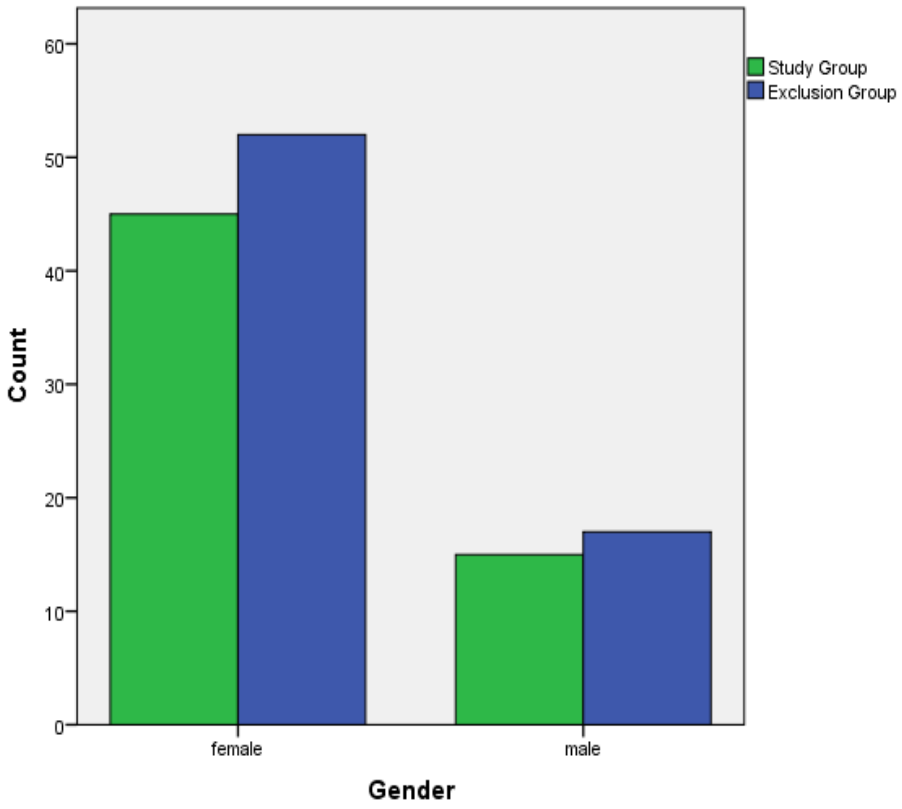

Figure 16 - Table and Graph Showing Gender Distribution Between SG and EG

The mean BMI of the SG was 50.4kg/m^2 with a SD 6.8kg/m^2. For the EG these figures were 48.3kg/m^2 and 6.6kg/m^2 respectively.

BMI	Study Group	Exclusion Group	Total
BMI≤40	3	5	8
40<BMI≤50	26	38	64
50<BMI≤60	28	22	50
60<BMI≤70	2	4	6
70<BMI≤80	1	0	1
Total	60	69	129

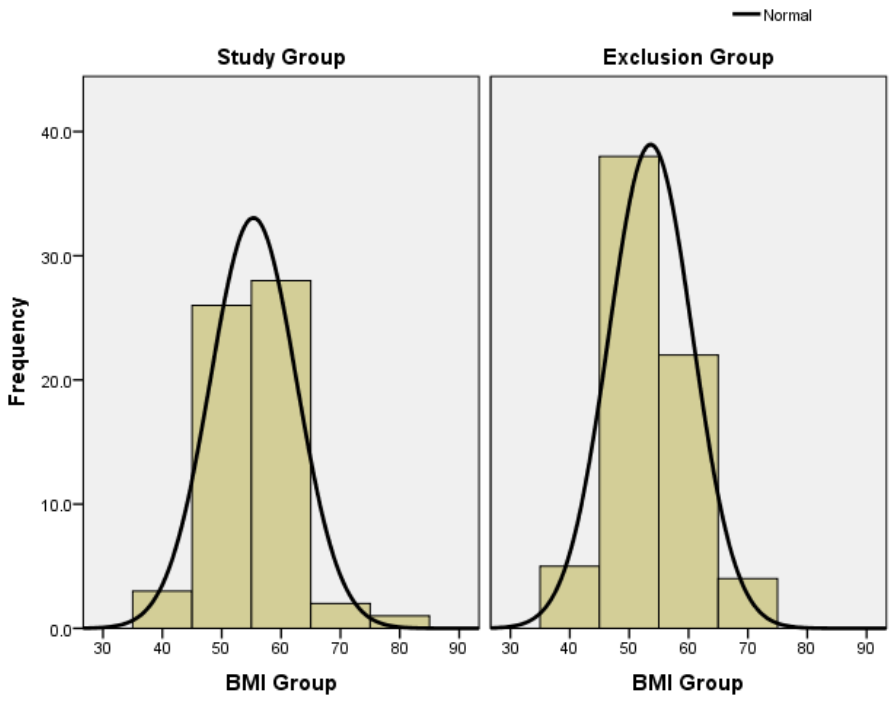

Figure 17 - Table and Graph Showing BMI Range Distribution Between SG and EG

The mean age of the SG was 42.2 years with a SD 10.9 years. For the EG these figures were 46.0 years and 11.9 years respectively.

Age of Patient	Study Group	Exclusion Group	Total
16-19	1	1	2
20-29	8	7	15
30-39	16	8	24
40-49	20	28	48
50-59	10	13	23
60-69	5	12	17
Total	60	69	129

Figure 18 - Table Showing Age Distribution in Terms of Decade of Life for Patients in SG and EG

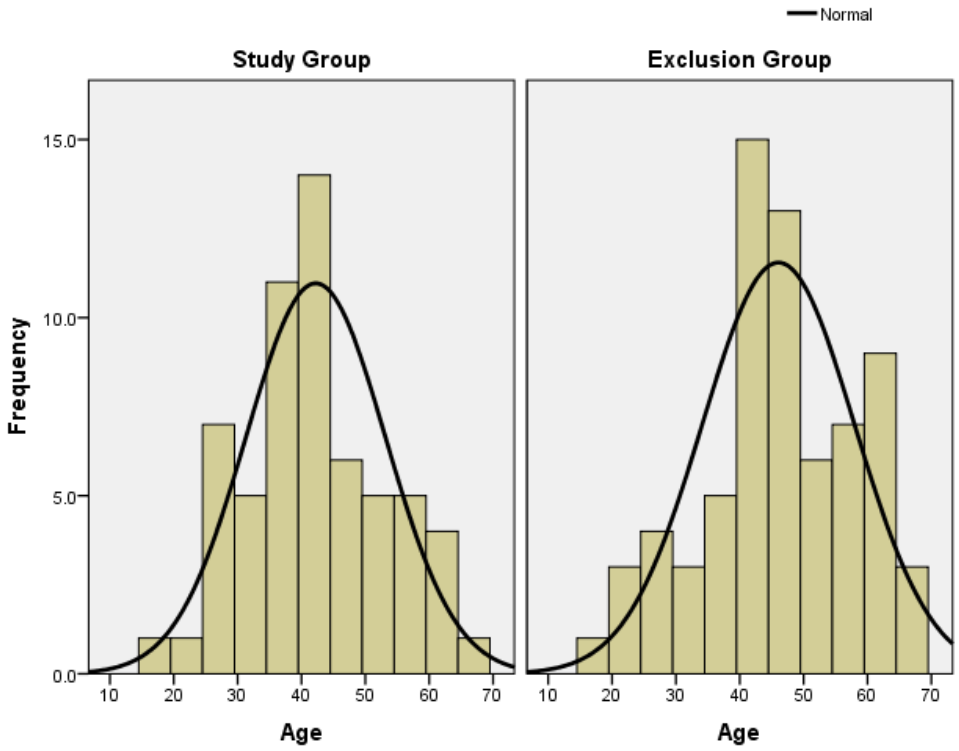

Figure 19 - Graph Showing Age Distribution of Patients in SG and EG

Primary Outcome Results for the Study Group

As shown in Figure 20 the SG achieved percentage eBMI losses ranging from 33.4% to 136.2% (mean 67.3%, SD 18.8%). The follow up duration ranged from 258 days to 838 days post-surgery (mean 405 days, SD 121days) with 46 out of the 60 patients (76.7%) having their follow up BW recorded within 100 days of the 1 year anniversary of their surgery.

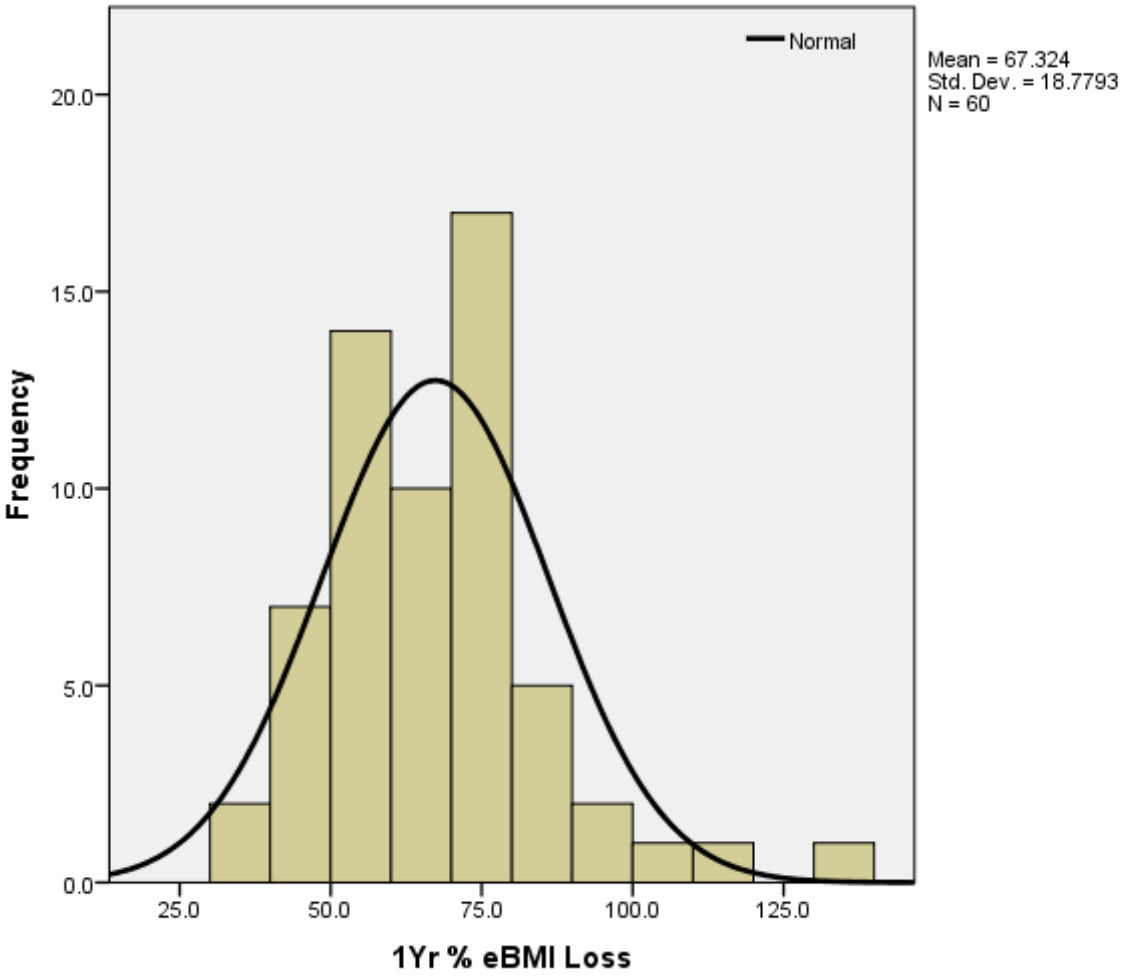

Figure 20 - Graph Showing Percentage eBMI Losses at 1 Year Post-RYGBP within SG

Analysis of the Impact of the Investigated Factors on the Primary Outcome using Linear Regression Analysis

The 13 investigated variables were analysed using linear regression analysis. As shown in figure 21 none of these factors were significantly associated with percent eBMI loss at 1 year.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	68.415	35.146		1.947	.058
	Genetic Risk	-.003	.133	-.004	-.025	.980
	Ethnicity	-3.834	4.097	-.132	-.936	.354
	Primary Reason	2.120	3.610	.087	.587	.560
	TFEQ R-18	.340	.440	.123	.773	.444
	Baecke	.346	.265	.225	1.304	.199
	Overall	-.004	.006	-.136	-.737	.465
	TIPI	.062	.364	.030	.170	.866
	urica_score	-3.296	2.129	-.226	-1.548	.128
	Alcohol	-.418	.468	-.132	-.894	.376
	Smoking	-2.648	3.397	-.117	-.780	.440
	Social Class	.342	1.756	.044	.195	.846
	Working Pattern	4.539	4.764	.220	.953	.346
	Comorbidity Score	.182	2.550	.011	.071	.943

a. Dependent Variable: 1Yr % eBMI Loss

Figure 21 - Tables Showing Linear Regression Analysis Results for the 13 Investigated Factors versus Percent eBMI Loss at 1 Year Post-RYGBP

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	4349.284	13	334.560	.935	.526[b]
	Residual	16457.775	46	357.778		
	Total	20807.059	59			

a. Dependent Variable: 1Yr % eBMI Loss

b. Predictors: (Constant), Comorbidity Score, Ethnicity, Smoking, Genetic Risk, Overall, Alcohol, urica_score, Primary Reason, TFEQ R-18, Social Class, Baecke, TIPI, Working Pattern

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.457[a]	.209	-.015	18.9150

a. Predictors: (Constant), Comorbidity Score, Ethnicity, Smoking, Genetic Risk, Overall, Alcohol, urica_score, Primary Reason, TFEQ R-18, Social Class, Baecke, TIPI, Working Pattern

Figure 21 (continued) - Tables Showing Linear Regression Analysis Results for the 13 Investigated Factors versus Percent eBMI Loss at 1 year Post-RYGBP

Analysis of the Impact of the Factor Component Sub-sets on the Primary Outcome Using Linear Regression Analysis

The component subsets of the 13 independent variables investigated were also analysed using linear regression analysis. The presence of IHD was excluded as a factor owing to the fact that none of the patients in the SG had been diagnosed with the condition. As shown in figures 22-24 these results echo those of the 13 primary factors in that only one component sub-set variable, the sport index measurement from the BPAQ, showed a significant association with the primary outcome ($p = 0.001$).

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	Sport Index	.	Stepwise (Criteria: Probability-of-F-to-enter <= .050, Probability-of-F-to-remove >= .100).

a. Dependent Variable: 1Yr % eBMI Loss

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.421[a]	.177	.163	17.1843

a. Predictors: (Constant), Sport Index

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	3679.624	1	3679.624	12.461	.001[b]
	Residual	17127.434	58	295.301		
	Total	20807.059	59			

a. Dependent Variable: 1Yr % eBMI Loss

b. Predictors: (Constant), Sport Index

Figure 22 - Tables Showing Linear Regression Analysis Results for the Factor Component Subsets versus Percent eBMI Loss at 1 Year Post-RYGBP

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	47.376	6.071		7.804	.000
	Sport Index	11.734	3.324	.421	3.530	.001

a. Dependent Variable: 1Yr % eBMI Loss

Figure 23 - Table Showing Linear Regression Analysis Results for the Included Factor Component Subsets versus Percent eBMI Loss at 1 Year Post-RYGBP

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Secondary Reason	-.080[b]	-.664	.510	-.088	.999
	Cognitive Restraint	.087[b]	.721	.474	.095	.987
	Uncontrolled Eating	.027[b]	.225	.823	.030	.996
	Emotional Eating	.018[b]	.152	.880	.020	.988
	Work Index	-.025[b]	-.204	.839	-.027	.965
	Leisure Time Index	.182[b]	1.524	.133	.198	.968
	Physical State	.007[b]	.055	.956	.007	.836
	Vitality	-.077[b]	-.619	.538	-.082	.924
	Relations	.102[b]	.834	.408	.110	.962
	Psychological	-.016[b]	-.128	.899	-.017	.962
	Extraversion	.002[b]	.019	.985	.002	.995
	Agreeableness	-.032[b]	-.263	.793	-.035	.982
	Conscientiousness	-.030[b]	-.240	.811	-.032	.944
	Emotional Stability	-.009[b]	-.079	.938	-.010	1.000
	Openness to Experiences	-.153[b]	-1.287	.203	-.168	.988
	Hypertension	-.020[b]	-.162	.872	-.021	.930
	Sleep Apnoea	-.009[b]	-.078	.938	-.010	.987
	COPD/ Asthma	-.062[b]	-.514	.609	-.068	1.000
	T2DM	.196[b]	1.642	.106	.213	.965
	PCOS	.033[b]	.267	.790	.035	.951
	Psych History	-.105[b]	-.879	.383	-.116	.996
	Sexual Abuse	.181[b]	1.517	.135	.197	.977
	Other Significant PMH	.038[b]	.309	.759	.041	.953

a. Dependent Variable: 1Yr % eBMI Loss

b. Predictors in the Model: (Constant), Sport Index

Figure 24 - Table Showing Linear Regression Analysis Results for the Excluded Factor Component Subsets versus Percent eBMI Loss at 1 Year Post-RYGBP

The linear relationship between the primary outcome and the BPAQ sport index is demonstrated in Figure 25. The line of best fit is shown as the unbroken line with the 95% confidence intervals being shown as the broken lines.

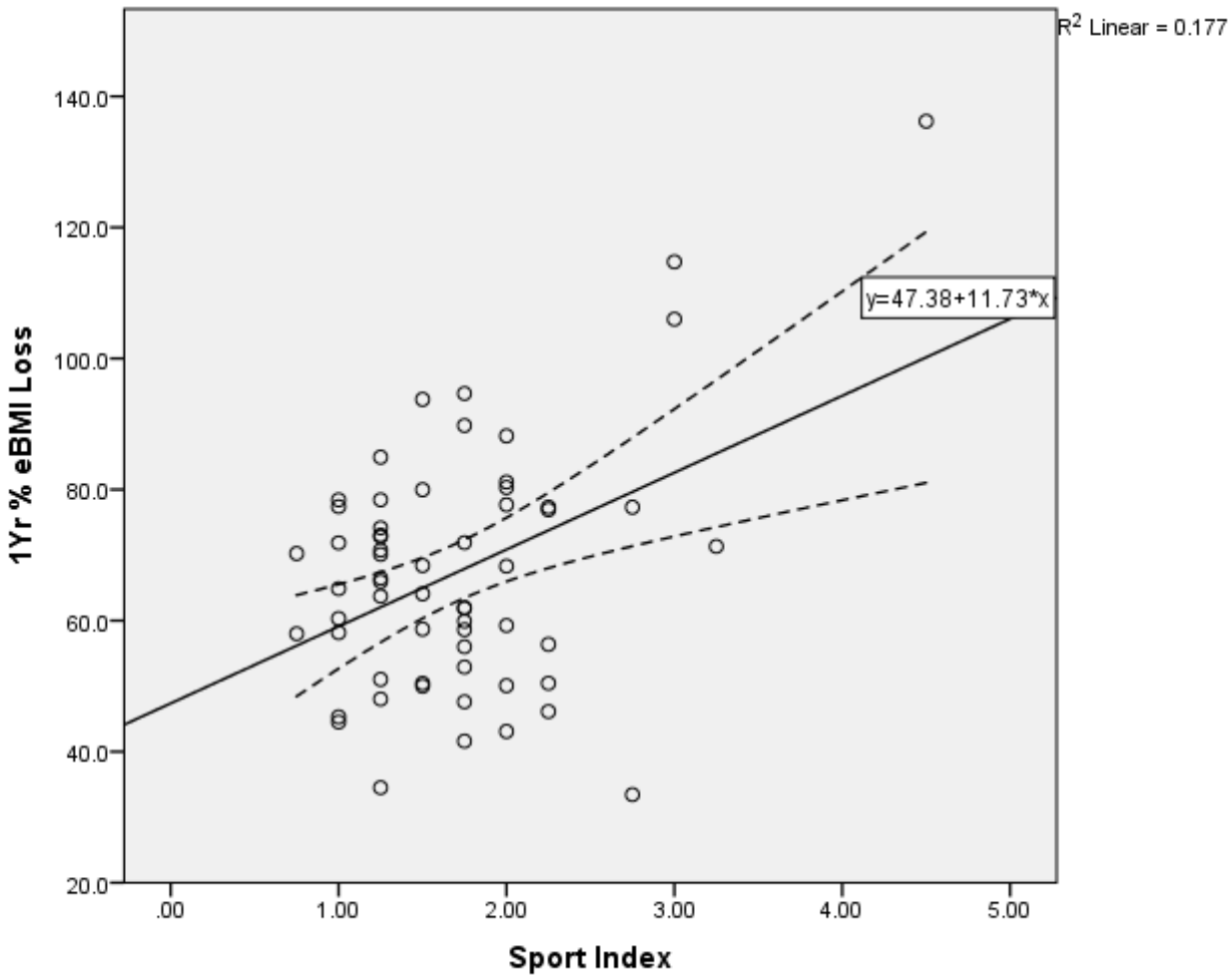

Figure 25 - Scatterplot Chart Showing Relationship Between BPAQ Sport Index and Percent eBMI Loss at 1 Year Post-RYGBP

Analysis of the Impact of the Investigated Factors on the Primary Outcome Using Binary Logistic Regression Analysis

Using the arbitrary cut-off point for a successful outcome of eBMI loss at 1 year post-RYGBP being greater than or equal to 70% the 13 investigated variables were re-analysed using binary logistic regression analysis. Figures 26 and 27 show that there were 27 patients (45%) in the SG who achieved this degree of eBWL and that the 13 variables combined failed to show a significant correlation with this degree of postoperative eBWL ($p = 0.178$). What is interesting however is that both the R-squared values ($R^2 = 0.418$ and 0.559) suggest that there is a trend towards a relationship between the 13 factors together and achievement of the cut-off point of 70% eBMI loss. Indeed inclusion of all 13 factors in the model is able to predict the outcome successfully 85% of the time. Additionally the individual factors of the TIPI score, overall URICA score and smoking status are all significantly associated with the outcome measure ($p = 0.013$, $p = 0.016$ and $p = 0.027$ respectively).

Classification Table[a,b]

			Predicted		
			1Yr % eBMI Loss >=70		
	Observed		Not Selected	Selected	Percentage Correct
Step 0	1Yr % eBMI Loss >=70	Not Selected	33	0	100.0
		Selected	27	0	.0
	Overall Percentage				55.0

a. Constant is included in the model.

b. The cut value is .500

Figure 26 - Table Showing Number of Patients in SG Whose Percent eBMI Loss at 1 Year Post RYGBP was Greater Than or Equal to 70%

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	32.475	26	.178
	Block	32.475	26	.178
	Model	32.475	26	.178

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	50.102[a]	.418	.559

a. Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.

Classification Table[a]

			Predicted		
			1Yr % eBMI Loss >=70		
	Observed		Not Selected	Selected	Percentage Correct
Step 1	1Yr % eBMI Loss >=70	Not Selected	29	4	87.9
		Selected	5	22	81.5
	Overall Percentage				85.0

a. The cut value is .500

Figure 27 - Tables Showing Results of Binary Logistic Regression Analysis of the 13 Investigated Factors

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	geneticr	-.017	.024	.490	1	.484	.983
	ethnicit(1)	25.951	40192.977	.000	1	.999	186299842058.049
	primaryr			.764	3	.858	
	primaryr(1)	-1.113	2.019	.304	1	.581	.328
	primaryr(2)	-1.365	1.679	.661	1	.416	.255
	primaryr(3)	-.842	1.743	.233	1	.629	.431
	tfeq18	.080	.089	.795	1	.372	1.083
	bpaq	.079	.055	2.095	1	.148	1.082
	osqol_overall	.003	.001	3.616	1	.057	1.003
	tipi	.251	.101	6.131	1	.013	1.286
	urica_score	-1.139	.474	5.773	1	.016	.320
	alcohol	-.098	.082	1.399	1	.237	.907
	smoke			7.242	2	.027	
	smoke(1)	4.457	1.725	6.675	1	.010	86.191
	smoke(2)	5.164	2.043	6.393	1	.011	174.929
	social			5.077	7	.651	
	social(1)	-2.374	2.317	1.050	1	.306	.093
	social(2)	-5.453	2.872	3.605	1	.058	.004
	social(3)	-3.905	2.078	3.532	1	.060	.020
	social(4)	-2.963	2.607	1.291	1	.256	.052
	social(5)	-2.283	2.079	1.206	1	.272	.102
	social(6)	-.965	1.835	.277	1	.599	.381
	social(7)	-2.481	2.616	.899	1	.343	.084
	pattern			.089	1	.766	
	pattern(1)	.453	1.517	.089	1	.766	1.572
	comorb			4.131	5	.531	
	comorb(1)	19.221	40193.032	.000	1	1.000	222590331.366
	comorb(2)	22.826	40193.032	.000	1	1.000	8187479039.644
	comorb(3)	21.057	40193.032	.000	1	1.000	1395638176.880
	comorb(4)	21.950	40193.032	.000	1	1.000	3410976639.282
	comorb(5)	22.448	40193.032	.000	1	1.000	5611508687.217
	Constant	-55.510	56841.493	.000	1	.999	.000

a. Variable(s) entered on step 1: geneticr, ethnicit, primaryr, tfeq18, bpaq, osqol_overall, tipi, urica_score, alcohol, smoke, social, pattern, comorb.

Figure 27 (continued) - Tables Showing Binary Logistic Regression Analysis Results for the 13 Investigated Factors

The binary logistic regression analysis was repeated using the same dependent variable but this time only including those investigated factors showing significance in the original model. As shown in figure 28 the exclusion of the other 10 factors reduced both the R^2 (the percentage of the variability in the data set accounted for by the model) (R^2 = 0.134 and 0.180) and the degree of significance (p = 0.372). Accordingly the accuracy of the model created from these 3 factors alone was only able to correctly predict the outcome 67% of the time as opposed to 85% when all 13 investigated factors were included. This suggests that there was some interaction between the 3 factors in this analysis and one or more of the excluded variables. The only group in this model showing significance are those patients who were active smokers at the time of recruitment (p = 0.045).

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	8.654	8	.372
	Block	8.654	8	.372
	Model	8.654	8	.372

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	73.922[a]	.134	.180

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

Figure 28 - Tables Showing Binary Logistic Regression Analysis Results for Model Including TIPI, URICA and Smoking Status Only

Classification Table[a]

			Predicted		
			1Yr % eBMI Loss >=70		
	Observed		Not Selected	Selected	Percentage Correct
Step 1	1Yr % eBMI Loss >=70	Not Selected	25	8	75.8
		Selected	12	15	55.6
	Overall Percentage				66.7

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	urica_score	-.519	.271	3.670	1	.055	.595
	smoke			4.042	2	.133	
	smoke(1)	1.538	.768	4.007	1	.045	4.656
	smoke(2)	1.418	.968	2.148	1	.143	4.129
	extravert	-.015	.113	.018	1	.893	.985
	conscience	.007	.101	.004	1	.948	1.007
	emotstab	.027	.109	.062	1	.803	1.027
	optoexp	.143	.129	1.238	1	.266	1.154
	agreeable	-.051	.114	.202	1	.653	.950
	Constant	2.975	3.291	.817	1	.366	19.583

a. Variable(s) entered on step 1: urica_score, smoke, extravert, conscience, emotstab, optoexp, agreeable.

Figure 28 (Continued) – Tables Showing Binary Logistic Regression Analysis Results for Model Including TIPI, URICA and Smoking Status Only

Analysis of the Impact of the Factor Component Sub-sets Using Binary Logistic Regression Analysis

The component subsets of the 13 investigated primary variables were also analysed using binary logistic regression analysis. As before IHD was excluded as a factor. As shown in figure 29 the model created using these variable does not show significance (p = 0.540) however it is able to correctly predict the outcome 83.3% of the time. As with the linear regression analysis the only factor showing significance is the sport index component of the BPAQ (p = 0.027).

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	25.623	27	.540
	Block	25.623	27	.540
	Model	25.623	27	.540

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	56.954[a]	.348	.465

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Classification Table[a]

			Predicted		
			1Yr % eBMI Loss >=70		
	Observed		Not Selected	Selected	Percentage Correct
Step 1	1Yr % eBMI Loss >=70	Not Selected	29	4	87.9
		Selected	6	21	77.8
	Overall Percentage				83.3

a. The cut value is .500

Figure 29 - Tables Showing Binary Logistic Regression Analysis Results for Factor Component Subsets

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	secondar			6.047	4	.196	
	secondar(1)	1.463	1.595	.841	1	.359	4.320
	secondar(2)	2.285	1.255	3.316	1	.069	9.823
	secondar(3)	2.988	1.605	3.465	1	.063	19.842
	secondar(4)	-.403	1.882	.046	1	.830	.668
	cogrestr	.174	.165	1.101	1	.294	1.190
	uncontro	-.117	.100	1.368	1	.242	.889
	emotiona	.243	.255	.903	1	.342	1.274
	workinde	.486	.370	1.729	1	.189	1.626
	sportind	1.631	.735	4.921	1	.027	5.107
	leisuret	.704	.750	.881	1	.348	2.022
	physical_state	.002	.003	.320	1	.572	1.002
	vitality	.000	.004	.003	1	.957	1.000
	relations	.016	.010	2.647	1	.104	1.016
	psychological	-.001	.004	.089	1	.766	.999
	extravert	-.035	.148	.056	1	.814	.966
	agreeable	-.179	.182	.971	1	.324	.836
	conscience	-.124	.156	.635	1	.426	.883
	emotstab	.259	.217	1.429	1	.232	1.296
	optoexp	.182	.174	1.093	1	.296	1.200
	bp(1)	.843	1.066	.626	1	.429	2.324
	osa(1)	-2.478	1.764	1.974	1	.160	.084
	copdasth(1)	.557	1.059	.277	1	.599	1.746
	diabetes(1)	-2.570	1.341	3.671	1	.055	.077
	psych(1)	-.203	1.090	.035	1	.852	.816
	sexabuse(1)	.269	1.211	.049	1	.824	1.309
	otherpmh(1)	.355	1.167	.092	1	.761	1.426
	pcos(1)	1.520	2.325	.427	1	.513	4.570
	Constant	-9.617	6.032	2.542	1	.111	.000

a. Variable(s) entered on step 1: secondar, cogrestr, uncontro, emotiona, workinde, sportind, leisuret, physical_state, vitality, relations, psychological, extravert, agreeable, conscience, emotstab, optoexp, bp, osa, copdasth, diabetes, psych, sexabuse, otherpmh, pcos.

Figure 29 (Continued) – Tables Showing Binary Logistic Regression Analysis Results for Factor Component Subsets

Secondary Outcome Results for the Study Group

Resolution of T2DM:

Of the 60 member of the SG only 15 (25%) had been diagnosed as having T2DM at the first outpatient appointment. Of these 3 (20%) were diet controlled and 12 (80%) were either on oral hypoglycaemic agents or insulin or both. Of the 12 patients on medication for T2DM preoperatively 9 (75%) had been discontinued by 1 year post RYGBP.

The mean preoperative HbA1c value for the patients without T2DM in the SG was 37.7mmol/mol (SD 6.9mmol/mol). None of this group had postoperative HbA1c measurements since doing such a test would be both illogical and of no clinical value not to mention invasive and expensive.

Those patients in the SG with diet-controlled T2DM were only 3 in number and one did not have a preoperative HbA1c measurement. The other 2 patients measured 25.7mmol/mol and 54.1mmol/mol. None of the 3 had postoperative HbA1c measurements.

As shown in figure 30 those 3 patients in the SG who were on medication for T2DM preoperatively and remained on medication postoperatively all had HbA1c measurements before and after surgery. Whilst there was a mean drop in HbA1c following surgery (18.5mmol/mol (SD = 15.1mmol/mol)) this was not statistically significant ($p = 0.169$) however of course meaningful interpretation of such a small sample size is impossible.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Preop HbA1c	59.900	3	16.1034	9.2973
	Postop HbA1c	41.367	3	4.4456	2.5667

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	Preop HbA1c & Postop HbA1c	3	.343	.777

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Preop HbA1c - Postop HbA1c	18.5333	15.1665	8.7564	-19.1424	56.2091	2.117	2	.169

Figure 30 - Tables Showing Paired t-test Analysis of Preoperative and Postoperative HbA1c Measurements in those Patients in SG with T2DM Who Required Tablets and/ or Insulin for their T2DM Both Before and 1 Year After RYGBP

Figure 31 shows that 8 of the 9 patients (89%) in the SG who were on medication for T2DM preoperatively and had discontinued their medication by 1 year postoperatively also had HbA1c measurements both before and after surgery. The mean drop in HbA1c following surgery of 17.9mmol/mol (SD = 12.4mmol/mol) in this group was however statistically significant (p = 0.005) though again the small sample size warrants caution.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Preop HbA1c	56.825	8	12.1941	4.3113
	Postop HbA1c	38.912	8	7.6810	2.7157

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	Preop HbA1c & Postop HbA1c	8	.286	.493

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Preop HbA1c - Postop HbA1c	17.9125	12.4167	4.3900	7.5318	28.2932	4.080	7	.005

Figure 31 - Tables Showing Paired t-test Analysis of Preoperative and Postoperative HbA1c Measurements in Those Patients in SG who Required Tablets and/ or Insulin for their T2DM Before RYGBP but Had Been Discontinued from These Medications by 1 Year Post-RYGBP

Resolution of Hypertension:

Of the 60 members of the SG only 14 (23%) were on treatment for hypertension preoperatively. Of the 46 patients without hypertension 8 had both preoperative and postoperative BP measurements. As shown in figure 32 significant reductions were seen in this group in terms of both mean systolic (18.4mmHg (SD = 18.3mmHg)) (p = 0.025) and diastolic (13.9mmHg (SD = 16.4mmHg)) (p = 0.048) blood pressures.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Preop Systolic	141.50	8	17.615	6.228
	Postop Systolic	123.13	8	9.172	3.243
Pair 2	Preop Diastolic	82.00	8	11.976	4.234
	Postop Diastolic	68.13	8	8.476	2.997

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	Preop Systolic & Postop Systolic	8	.179	.671
Pair 2	Preop Diastolic & Postop Diastolic	8	-.265	.527

Figure 32 - Tables Showing Paired t-test Analysis of Preoperative and Postoperative BP Measurements in Those Patients in SG Who Were Not on Medication for Hypertension Preoperatively

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Preop Systolic - Postop Systolic	18.375	18.345	6.486	3.038	33.712	2.833	7	.025
Pair 2	Preop Diastolic - Postop Diastolic	13.875	16.401	5.799	.164	27.586	2.393	7	.048

Figure 32 (Continued): Tables Showing Paired t-test Analysis of Preoperative and Postoperative BP Measurements in Those Patients in SG Who Were Not on Medication for Hypertension Preoperatively

Of the 14 patients with preoperative hypertension only 5 (35.7%) had been discontinued from all forms of antihypertensive medication at 1 year post-RYGBP whereas 9 (64.3%) were still taking at least 1 such drug. Of these 9 preoperative and postoperative BP measurements were available for 8. As shown in figure 33 this group, whilst still requiring antihypertensive medication, experienced a significant drop in systolic BP following surgery (mean 16.5mmHg (SD = 14.5mmHg)) (p = 0.015) but no significant drop in diastolic BP (mean 4.6mmHg (SD = 7.0mmHg)) (p = 0.103). It is worth noting that the correlation in this this subgroup for the systolic BP drop (0.738) is much greater than for the other significant results meaning that in this subgroup those patients with high systolic BP measurements preoperatively tended to also be the ones with high systolic BP measurements postoperatively.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Preop Systolic	140.88	8	20.698	7.318
	Postop Systolic	124.38	8	11.363	4.018
Pair 2	Preop Diastolic	78.75	8	6.861	2.426
	Postop Diastolic	74.13	8	5.463	1.931

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	Preop Systolic & Postop Systolic	8	.738	.037
Pair 2	Preop Diastolic & Postop Diastolic	8	.375	.361

Figure 33 - Tables Showing Paired t-test Analysis of Preoperative and Postoperative BP Measurements in Those Patients in SG Who Were on Medication for Hypertension Preoperatively and Remained on it 1 Year Post-RYGBP

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Preop Systolic - Postop Systolic	16.500	14.511	5.130	4.368	28.632	3.216	7	.015
Pair 2	Preop Diastolic - Postop Diastolic	4.625	6.989	2.471	-1.218	10.468	1.872	7	.103

Figure 33 (continued): Tables Showing Paired t-test Analysis of Preoperative and Postoperative BP Measurements in Those Patients in SG Who Were on Medication for Hypertension Preoperatively and Remained on it 1 Year Post-RYGBP

Figure 34 shows the results for the remaining 5 patients who were discontinued from all antihypertensive medications by 1 year post-RYGBP. Whilst there is a drop in both systolic and diastolic BP following RYGBP in this group the small sample size and wide SD mean that neither figure is statistically significant (p = 0.361 and p = 0.398 respectively).

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Preop Systolic	162.20	5	47.788	21.371
	Postop Systolic	130.80	5	28.969	12.955
Pair 2	Preop Diastolic	91.80	5	25.704	11.495
	Postop Diastolic	78.00	5	15.508	6.935

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	Preop Systolic & Postop Systolic	5	-.545	.342
Pair 2	Preop Diastolic & Postop Diastolic	5	-.206	.740

Figure 34 - Tables Showing Paired t-test Analysis of Preoperative and Postoperative BP Measurements in Those Patients in SG Who Were on Medication for Hypertension Preoperatively and Were Discontinued From it 1 Year Post-RYGBP

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Preop Systolic - Postop Systolic	31.400	68.057	30.436	-53.104	115.904	1.032	4	.361
Pair 2	Preop Diastolic - Postop Diastolic	13.800	32.637	14.596	-26.725	54.325	.945	4	.398

Figure 34 (continued): Tables Showing Paired t-test Analysis of Preoperative and Postoperative BP Measurements in Those Patients in SG who Were on Medication for Hypertension Preoperatively and Were Discontinued From it 1 Year Post-RYGBP

Analysis of the Impact of the Investigated Factors on the Secondary Outcomes

As shown in figures 35 and 36 binary logistic regression analysis failed to yield any significant associations between the 13 primary investigated factors and the discontinuation of either hypoglycaemics or insulin in patients with T2DM preoperatively or antihypertensives in those on medication for hypertension preoperatively.

Classification Table[a,b]

			Predicted		
			T2DM Medications Stopped		Percentage Correct
	Observed		No	Yes	
Step 0	T2DM Medications Stopped	No	0	3	.0
		Yes	0	9	100.0
	Overall Percentage				75.0

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	1.099	.667	2.716	1	.099	3.000

Figure 35 - Tables Showing Binary Logistic Regression Analysis Results for the 13 Investigated Factors Versus Discontinuation of T2DM Medications at 1 Year Post-RYGBP

Variables not in the Equation[a]

			Score	df	Sig.
Step 0	Variables	geneticr	.081	1	.776
		primaryr	4.000	3	.261
		primaryr(1)	.800	1	.371
		primaryr(2)	3.273	1	.070
		primaryr(3)	.000	1	1.000
		tfeq18	.050	1	.823
		bpaq	3.824	1	.051
		osqol_overall	3.214	1	.073
		tipi	2.089	1	.148
		urica_score	.752	1	.386
		alcohol	.278	1	.598
		smoke	2.400	2	.301
		smoke(1)	1.333	1	.248
		smoke(2)	2.000	1	.157
		social	4.889	3	.180
		social(1)	3.273	1	.070
		social(2)	.800	1	.371
		social(3)	1.333	1	.248
		pattern	.622	2	.733
		pattern(1)	.114	1	.735
		pattern(2)	.364	1	.546
		comorb	7.429	4	.115
		comorb(1)	.364	1	.546
		comorb(2)	.364	1	.546
		comorb(3)	1.029	1	.310
		comorb(4)	7.200	1	.007

a. Residual Chi-Squares are not computed because of redundancies.

Figure 35 (continued): Tables Showing Binary Logistic Regression Analysis Results for the 13 Investigated Factors Versus Discontinuation of T2DM Medications at 1 year Post-RYGBP

Classification Table[a,b]

			Predicted		
			BP Medications Stopped		Percentage
	Observed		no	yes	Correct
Step 0	BP Medications Stopped	no	9	0	100.0
		yes	5	0	.0
	Overall Percentage				64.3

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	-.588	.558	1.111	1	.292	.556

Figure 36 - Tables Showing Binary Logistic Regression Analysis Results for the 13 Investigated Factors Versus Discontinuation of BP Medications at 1 Year Post-RYGBP

Variables not in the Equation[a]

			Score	df	Sig.
Step 0	Variables	geneticr	.353	1	.553
		primaryr	1.950	2	.377
		primaryr(1)	.598	1	.439
		primaryr(2)	1.593	1	.207
		tfeq18	3.089	1	.079
		bpaq	1.849	1	.174
		osqol_overall	1.292	1	.256
		tipi	.093	1	.760
		urica_score	.001	1	.979
		alcohol	1.574	1	.210
		smoke	.363	2	.834
		smoke(1)	.311	1	.577
		smoke(2)	.009	1	.923
		social	3.111	5	.683
		social(1)	.598	1	.439
		social(2)	.009	1	.923
		social(3)	.207	1	.649
		social(4)	1.593	1	.207
		social(5)	1.296	1	.255
		pattern	.871	2	.647
		pattern(1)	.311	1	.577
		pattern(2)	.207	1	.649
		comorb	3.656	4	.455
		comorb(1)	.207	1	.649
		comorb(2)	1.938	1	.164
		comorb(3)	.026	1	.872
		comorb(4)	1.296	1	.255

a. Residual Chi-Squares are not computed because of redundancies.

Figure 36 (continued) - Tables Showing Binary Logistic Regression Analysis Results for the 13 Investigated Factors versus Discontinuation of BP Medications at 1 year Post-RYGBP

Chapter 8 – Discussion and Conclusions

Development of a Predictive Scoring System

As discussed in chapter 6 the secondary aim of this study was to attempt to devise a scoring system for use in the preoperative setting with a view to identifying those patients most likely to experience a beneficial result in terms of weight loss or comorbidity resolution. With regard to postoperative eBWL, due to the SG consisting of only 60 patients, these data are insufficiently powered to be able to confidently construct such a predictive tool using either CART analysis or an artificial neural network. Similarly, as discussed in chapter 2, for linear regression the independent variables need to show significance before their ORs can be used to assign weights to the variables to be used in the scoring system. Although it may be that the BPAQ, or more specifically the sport index component of the BPAQ, could form the basis of such a tool a much larger SG would be required to confirm this. The finding that by both linear and logistic regression analyses the sport index is significant would make some clinical sense – it follows logically that those patients who were morbidly obese despite engaging in a lot of physical exercise prior to surgery would continue such activities postoperatively and would be more likely to experience a favourable result. That said a quick look at figure 25 clearly shows that the majority of patients in the SG scored between 1 and 2 and that only a small proportion were in the high sport index category.

When one considers that the secondary outcome SG sizes were 12 and 14 patients for T2DM and hypertension respectively it would seem presumptive to even begin to comment on emerging trends. A strongly significant *p* value for any factor in such an under-recruited study is highly suspicious of a type 1 error (positive by chance rather than in reality). However, the aims of developing a scoring system could have been achieved were it not for the recruitment difficulties encountered after the commencement of this phase of the study.

Secondary Outcomes

The overall antihypertensive discontinuation rate in this SG is disappointingly low compared to the literature. It should, however, be borne in mind that whilst the actual reductions in systolic and diastolic BP shown in figure 34 (162.2mmHg preoperatively to 130.8mmHg postoperatively and 91.8mmHg preoperatively to

78.0mmHg postoperatively respectively) although not *statistically* significant (small sample size notwithstanding) these reductions may be enough to be *clinically* significant though clearly this is only something that could be assessed with a much greater sample size and follow up period.

Strengths of the Study

1) The study was performed as a multicentre study thus reducing the risk of institutional biases with regard to the results.

2) The study was conducted in a prospective manner thus avoiding the biases inherent with retrospective studies.

3) The study was designed to answer a specific clinical need in that to have a tool able to accurately identify which patients would gain the best result following RYGBP would be useful.

4) The study was designed with a specific end-point in mind, namely a cost effective, user-friendly predictive tool that could be applied as early as possible in the patient journey thereby minimising inefficiency.

5) The study showed that such an approach to the development of a predictive tool is feasible and viable.

Limitations of the Study

1) As previously stated, the primary weakness of this study relates to the lack of numbers. In order to confidently draw any conclusions a minimum of 10 patients needed to have been in the SG for each independent factor being investigated. Ideally for linear regression analysis each of the nominal and ordinal variables should contain more than 50 patients although this clearly would require the study to be done on a much larger scale. Since the SG consisted of only 60 patients for the primary outcome and 12 and 14 patients for the two secondary outcomes then it is clearly underpowered. It is however interesting that not one of the independent factors used produced a significant result for the primary outcome given that the majority were

selected on the basis of having been found to have either a significant positive or negative association with eBWL in the literature as described in chapter 3.

2) The paucity of significant results may be an unexpected consequence of the second main criticism of the study. BW has been shown to fall fairly steadily following RYGBP beginning in the immediate postoperative phase and continuing until 12 to 24 months post-surgery.(500-502) This is why the majority of the literature reports outcomes at either 1 or 2 years. In other forms of bariatric surgery, notably the gastric band, the weight loss is more gradual and a plateau is reached between 2 and 3 years. For all bariatric operations the plateau phase is followed by a natural gradual increase in BW. Owing to restrictions regarding the amount of time in which this study had to be completed a 12 month follow up period was the realistic maximum that could be achieved. It may be that with a longer follow up period, particularly with greater patient numbers, more significant findings could have been unearthed.

3) On a similar note it is undoubtedly a weakness of the study that it proved to be impossible for precise follow-up measurement dates to be used. Ideally, 1 year follow-up BW, HbA1c and blood pressure recordings should be obtained on the 1 year anniversary of surgery, or at least within a narrow time-window either side of that date, however these follow-up appointments were dependent on factors outwith the control of the investigative team such as clinic co-ordinators, clinic date availabilities, patient attendance etc. For this reason it was felt that the method of using the data recorded "nearest to the 1 year anniversary of surgery but after the 250 day minimum" was adopted. This was felt to be a less-than-ideal but acceptable and pragmatic solution since our own data, as well as the published literature, suggest that following RYGBP weight loss begins to plateau at around this time with 85-90% of the ultimate eBWL having been achieved at this point.(503) 85-90% was felt to be "close enough" for us to obtain both reasonably satisfactory BW recordings whilst simultaneously maximising the number of patients with data amenable to analysis. Of course, by implementing specific milestones into the study design the effect of this avoidable source of potential bias and

inaccuracy could have been avoided altogether. It is worth noting, however, that this is only an issue with regard to the primary outcome since the literature shows that glycaemic and hypertensive changes do not follow the same gradual change as is seen in eBWL.

4) The tools used for this study were selected on a number of factors – chief among these were that they needed to be free to use, quick to complete and relatively easy to score and interpret. These three criteria were felt to be essential since the object of the study was to develop a preoperatively administered test which could be used in a primary care or outpatient setting in order to select those patients most likely to achieve a successful result from RYGBP surgery. It was felt that those psychological tools requiring the purchase of a licence would be too expensive to obtain and on a large scale basis and those tools which either took a long time to complete or interpret would be either poorly filled in by the target population or impractical for use in an outpatient setting. That said, several of the tools had their own individual limitations which may have influenced the results of the study:

    a. Thirlby & Randall's obesity risk index study was devised to quantify the genetic contribution to an individual's weight.(492) It was not devised with a view to predicting the outcome of bariatric procedures. It was included in this study was to see if it could be used in this way and because it met the three essential criteria described above. During the course of the study it became apparent that many of the recruited patients had difficulties answering the questions either because they could not recall their approximate heights or weights at the 3 age milestones or because they could not recall or estimate the same measurements for their parents, siblings or second degree relatives. Additionally patients who did not know one or both of their parents and those who were only children may have had artificially low scores. A further drawback to this tool was that many patients had relatives who had experienced wide fluctuations in their weight during their lives and so scoring the BMIs of such people became an exercise in futility as well as guesswork.

As was discussed in chapter 1, recent years have seen a huge increase in our understanding of those genes predisposing to the overweight or obese phenotype.(504-507) As one would expect, following on the heels of this we have seen an increase in the literature available examining the effects of these genes on bariatric procedures and vice versa.(508-511) Although it has yet to be conclusively shown which, if any, of the commonly recognised gene variants predisposing to obesity are associated with better or worse BWL following RYGBP it may be that the identification of one or two of the more common genes, such as the FTO or MC4R genes, would be a preferable method of determining the genetic predisposition towards obesity in the pre-RYGBP population. The two major drawbacks to this would be the facts that any predictive tool generated which utilised genetic testing would no longer be free to perform and or quick to complete, both of which were key objectives.

b. Although it has produced the only significant result the BPAQ was generally a poorly completed questionnaire. The reason for this lay in the fact that many of the recruited patients were either retired, incapacitated or not in employment. Oftentimes this was a consequence, either directly or indirectly, of the obesity for which they were seeking treatment. As a result questions 1-8 (the work index) was felt to be difficult to answer and confusing and this is likely to have resulted in the extremely skewed work index frequency chart seen in Figure 37.(495) The normal distribution curve is shown as the solid black line to highlight the degree of skewness. Having said this it should be noted that the sport and leisure time indices as well as the overall BPAQ did not show a significant degree of skewness and so the effect of the work index should not be overstated.

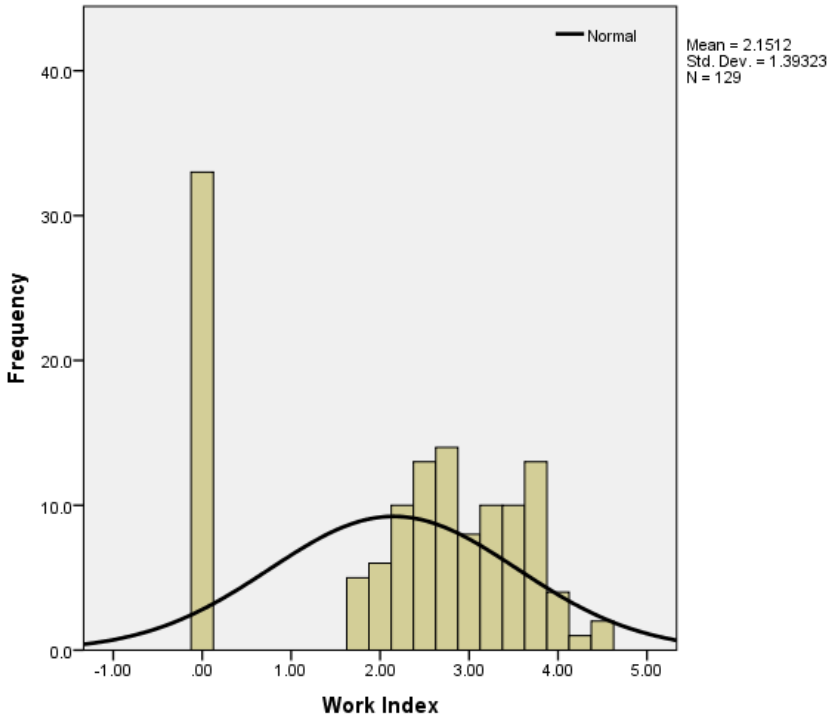

Figure 37 - Histogram Showing Frequency of Work Index Component Scores from the BPAQ

c. Although not a flaw with the TIPI as such it is important to remember that the concept of an overall "personality score" should be interpreted with caution from a psychological point of view.(497) The 5 component subsets of the TIPI refer to the so-called "Big Five" personality domains which are distinct entities and whilst to combine them for the purposes of this study might be convenient and interesting it is nevertheless a psychological nonsense.

d. The URICA was, like the BPAQ, generally felt to be a difficult questionnaire to answer.(499) Many patients felt that it was too long and that the wording was confusing, however, since the URICA was generally the last questionnaire answered by the patients, this may have been a consequence of mental fatigue on the part of the patients. This would support the policy of choosing the smallest number and most "user-friendly" psychological tools available. Another question regarding the concept of readiness to change is whether or not it alters

during a patient's preoperative journey. For example patients making tentative enquiries about bariatric surgery in general may have very different scores to those who have thoroughly researched the topic. Similarly those at the start of their preoperative journey may differ from those in the final few days before surgery. In the SG the delay from recruitment to surgery ranged from 41 days to 677 days with a mean average of 252 days – plenty of time for a patient to either "psyche themselves up" for surgery or get cold feet about it.

In addition to the limitations pertaining to individual tools listed above the issue of non-purposeful responding is a potentially confounding factor which could be applicable to all of the psychological questionnaires and indeed any of the other studied factors which required the recruited patients to provide a subjective response e.g. primary reason for wanting surgery etc.

5) The reasons for a patient seeking surgery were felt to be an important part of the process for assessing whether or not a patient was sufficiently motivated to undergo RYGBP and adopt the lifestyle and dietary changes necessary to achieve a desirable result. In practicality, however, it was a difficult factor to assess as very little literature exists on this topic and consequently the options available to respondents were those that were felt to be the most frequently cited reasons in the experience of the investigative team. Patients were asked an open question such as "What reason would you give if someone asked you why you wanted this surgery?" and their response was then matched to the option that most closely fitted the answer given. Whilst this method might be a convenient and feasible one it may also be that an alternative approach could have yielded markedly different data.

6) Smoking history, as discussed in chapter 3, has not been conclusively shown to be related to BWL following bariatric surgery.(269, 298, 304) The reason for the inclusion of alcohol intake and smoking history in this study was simply to see if there would be any correlation between the ability to stop or avoid these addictive activities and the ability to lose BW after RYGBP. Clearly this assumes that BWL following RYGBP is largely due to the

cessation of unhealthy habits (over-eating, poor diet etc) and the adoption of healthy ones (improved diet, greater physical activity etc). This is, of course, a considerable assumption and should such a correlation have been found to support this it is likely that the true mechanism of the relationship would have been far more complex. Given the potential of abstinence and smoking cessation to act as markers for the ability to adopt and sustain a healthier lifestyle it is possible that whilst no correlation was seen in this study a more detailed assessment could unearth a link. That said, the only factor found to be significant in the binary logistic regression analysis was the status of being an active smoker at the time of recruitment. As with the other factors a greater sample size would be necessary to confirm this finding.

With regard to alcohol consumption it may be worthwhile adopting a more categorical approach, similar to smoking status, as 48 of the SG (80%) were non-drinkers which firstly makes its inclusion as a scale variable questionable and secondly begs the question how many of those tee-totallers used to drink and had stopped by the time of recruitment.

7) Social class is known to be associated with the prevalence and prognosis of a wide variety of conditions including obesity which is well established as being more prevalent in the lower social classes.(512-515) The inclusion of social class in this study as a potentially predictive factor was to see if those from a less advantaged socioeconomic background were also less likely to experience a favourable result following RYGBP. One of the problems encountered however was that a significant number of those within the SG were limited in their employment options as a result of their comorbidities secondary to their obesity. It is possible that this may have biased the results although when one looks at Figure 38 it does seem credible to say that social class is not a factor when it comes to the primary outcome.

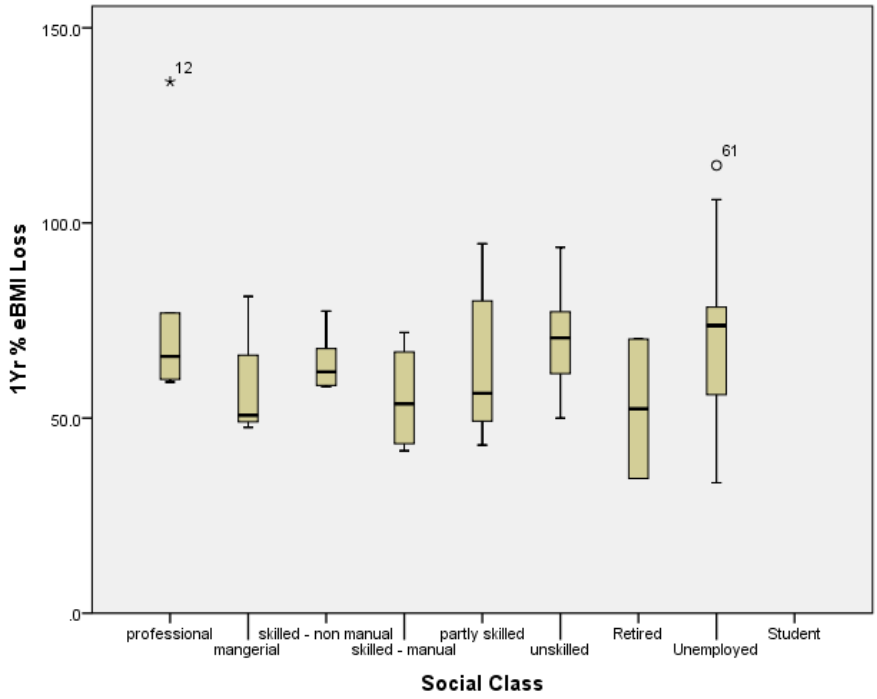

Figure 38 - Boxplot Showing Percent eBMI Loss at 1 Year Post-RYGBP Versus Social Class

8) The co-morbidity score was determined according to how many of the listed co-morbidities a recruited patient was known to have at the time of presentation and recruitment. One of the weaknesses of this aspect of the study was that a small number of patients were subsequently diagnosed with additional co-morbidities during the course of their pre-operative workup. In particular T2DM and OSA were diagnosed in several patients after recruitment. In addition the cumulative nature of the co-morbidity score implies that each of the conditions carries and equal impact which is unlikely to be the case. Having said this to reliably weight the conditions against each other would be extremely difficult due to the diversity of the range of conditions encountered in terms of severity, chronicity, duration, disease course, treatment etc. Although a simplistic cumulative score is an easy way round these issues it may well have led to a degree of inaccuracy in the final results.

9) The lack of variation in ethnicity was something of a disappointment, albeit a predictable one given the location of the study. Although attempts were

made to recruit from areas with a greater range of ethnic diversity this unfortunately proved impossible. As discussed in chapter 3 the literature clearly shows that some ethnic groups lose more weight post-bariatric surgery than others and so any scoring system attempting to predict such an outcome would need to take account of this. It is unfortunate however that the populations served by the institutions conducting the study have very little ethnic diversity. Attempts to address this issue by incorporating other institutions with less uniformity in their population sadly did not bear fruit. In some ways though it could be argued that it was something of a blessing not to be able to incorporate ethnicity into a patient selection tool as its inclusion would bring with it ethical implications regarding the selection or non-selection of patients, at least in part, according to their race. Similar ethical issues would also be encountered if such a tool were to utilise some of the other factors discussed in chapter 3 for example age, educational status, gender and marital status.

10) Since the primary outcome in the study was BWL the factors selected for study were chosen either on the basis of having been shown to have an association with this outcome or to see if such a relationship would exist. It could be argued therefore that these factors were not appropriate for the secondary outcomes and that factors specific to T2DM and BP should have been incorporated to add some legitimacy to any significant outcomes that may have been detected in this part of the study.

11) With regard to the secondary outcomes it is a considerable oversight in the method that objective measurements of glucose homeostasis and BP were not built in to the protocol for each patient and that they were not done at predetermined intervals. In particular it was an oversight that random single readings were utilised for BP recordings when it is well documented in the literature that more reliable measurements can be obtained either with 24-hour ambulatory BP monitors or even repeated home BP measurements using relatively inexpensive electronic sphygmomanometers available from most high-street pharmacies.(516, 517) This may have yielded some interesting data and would have increased the numbers available for analysis particularly

with regard to the control groups (those without either T2DM or hypertension preoperatively). The rationale for not obtaining these data in this manner was that it was felt that some patients may have been deterred from participating in the study if they thought that doing so might result in the need for additional blood tests and trips to either their GP practice or the hospital. In hindsight this was probably something that could have been overcome since blood tests are an essential part of both the preoperative work-up and of the postoperative care for all bariatric procedures. Whilst supplying home BP monitors to each of the recruited patients would undoubtedly have incurred a considerable expense it could be argued that what would be saved in terms of expenditure would more than have been gained in terms of scientific validity.

12) It is also a weakness in the method that the drug doses and indications were not recorded as these may have provided some interested data in themselves and may even have had a considerable impact on the results. For example it is not known how many of the patients on anti-hypertensives preoperatively whose BP medications were not stopped at 1 year were still on those medications because they were being taken for another condition such as cardiac arrhythmias etc.

<u>Suggestions for Modifications to the Method</u>

Although no scoring system could be devised from these data it remains the assertion of the investigators that the development of a preoperative screening tool for the purpose of targeted patient selection prior to RYGBP is still an avenue of research worth pursuing. If nothing else this study demonstrates that it would be feasible to conduct a study pooling a variety of potentially significant variables with a view to subsequently weighting them against one another but that the institution carrying it out would need to serve a population with a wider ethnic range and ideally would need to perform a much greater number of RYGBP procedures per year. If repeating this study at such an institution I would propose the following modifications to the method with a view to minimising some of the limitations listed above:

1) As previously mentioned an emphasis would need to be placed on being able to achieve greater numbers of patients in a timely fashion. This could be

achieved if necessary by recruiting from additional centres but this in turn would necessitate the need for some assurance of the uniformity of practices between institutions.

2) With greater numbers of patients the potential to use other forms of clinical prediction such as those discussed in chapter 2 becomes feasible. In particular ANN (as was the original intention of this study) and CART analysis should be incorporated into the method as part of the data analysis.

3) All outcome measures should be collected at fixed time points in the patients' postoperative journeys with as narrow variations as possible either side of these specified dates. For example, for postoperative BW measurements 1 year plus or minus 1 month, ideally with repeat measures with similarly narrow windows of opportunity at additional milestones such as 2 years or 5 years to allow for the studying of more long-term outcomes. This could be achieved simply by ensuring that those patients within the study are identified and, where feasible, booked into clinics well in advance with instructions to those staff organising outpatients clinics for these patients not to be cancelled or rescheduled for appointments outside of their window of opportunity.

4) Recruitment centres should reflect a wider diversity of ethnic backgrounds so that this factor could be properly assessed in a repeat study.

5) The practice of pigeon-holing the patients' primary reason for wanting surgery should be abandoned. Instead I would ask the patients to score the listed reasons for wanting surgery on a visual analogue scale from 0 to 10 (0 being not applicable, 10 being very applicable) to try to create a greater degree of comparability and objectivity though this statement in itself would require subsequent validation to ensure that it is true.

6) Prior to repeating the study it would be beneficial to re-evaluate which psychological tools most closely meet the criteria of being free to use, quick to complete and easy to administer and interpret. Whilst it may be that those tools used in this study are the optimal ones it is not unreasonable to want to

ensure that this is the case. Additionally it would be an interesting study to repeat the psychological evaluations at various points in the patient journey such as in the days prior to surgery and at one year postoperatively. As previously mentioned it is possible that one's URICA status would change between the time of first referral and surgery.

7) Objective measures of glucose homeostasis and BP (such as HbA1c and 24-hour BP monitoring respectively) should be obtained at recruitment, preoperatively and at the 1, 2 and 5 year milestones in all patients involved in the study including the control group. Additionally the types, indications for, and doses of, all T2DM and BP medications should be recorded.

8) For those patients known at recruitment to have T2DM or hypertension the duration of the condition (years since diagnosis) should be recorded.

9) Alcohol intake should be reclassified along the lines of smoking status into lifelong non-drinker, drinker and former drinker.

Summary

If taken at face value these data would suggest that with the exception of the sport index component of the BPAQ no preoperatively determinable factors consistently predicted the degree of BWL at 1 year following RYGBP and that no factors predicted T2DM or hypertension remission at the same stage. The number of patients in the SG however prevents any conclusions from being confidently drawn.

Although the amount of data available for analysis proved to be too small to devise the patient selection screening tool originally hoped for, this study does show that in a centre with a greater patient turnover such a study could be performed. This study also demonstrates that a multifactorial approach to clinical prediction is both possible and practical. In addition several flaws in the method were found during the course of this study which could easily be corrected to lend greater scientific credibility to the outcomes if repeated. As such, this study could be viewed as a valuable pilot or feasibility study – the fact that, through no fault with the study design itself, insufficient patient numbers were recruited to draw any confident conclusions should not be a deterrent to repeating the study at a larger centre in the future.

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Appendices

Appendix 1: Data Collection Sheet (shaded areas to be completed in clinic)

Confidential Study Number:			
DOB:	Age:	Gender: M / F	Height (m):
At First OPD appointment Weight (kg):	Waist (cm):	Hip (cm):	Neck (cm):
Waist/ Hip Ratio:	BMI:	eBMI:	
Estimated % body fat (Deurenberg):		Distribution: Android / Gynaecoid	
BMI Age 10: <23 23-26 or "very obese" ≥26 or "fattest kid in class" BMI Age 20: <30 30-40 >40 BMI Age 30: <35 35-50 >50 (or at time of presentation if age <30)			
Father's BMI: <30 30-40 >40 Mother's BMI: <30 30-40 >40 Siblings' Mean BMI: <30 30-40 >40 Number of 2nd degree relatives with BMI>35: 0 1 2 3 4 ≥5			
Ethnicity:		Generation in UK (if applicable):	
Partner's height (m): N/A		Partner's weight (kg): N/A	
Partner's BMI:		Partner's eBMI:	
Primary reason for seeking bariatric surgery: (please circle) Increase/ Improve: Life expectancy Quality of life Comorbidities Physical appearance Other (specify):			
Secondary reason for seeking bariatric surgery if applicable: (please circle) Increase/ Improve: Life expectancy Quality of life Comorbidities Physical appearance Other (specify):			
TFEQ R-18 □ Baecke Physical Activity Questionnaire □ Obese Specific Quality of Life □ Ten Item Personality Inventory □ URICA □		Score: Score: Score: Score: Score:	
Units alcohol/ week:		Smoking Hx: Never Current (Amount): Ex-smoker (Yrs stopped): Pack-years:	
Drug History:			

Social Class: 1 (Professional) 2 (Managerial) 3a (Skilled – non manual) 3b (Skilled – manual) 4 (Partly skilled) 5 (Unskilled) 6 (Other)
Working pattern: N/A(Yrs unemployed:) Shifts (Full/ Partial) Full-time Part-time

Operation Date:	Type of Surgery:	
Weight at surgery:	BMI (eBMI) at Surgery: ( )	
Comorbidities (years since diagnosis): IHD ( ) Hypertension ( ) Sleep apnoea ( ) COPD/ asthma ( ) BP ( ) / Other cardiorespiratory (specify): Diabetes ( ) PCOS ( ) Psychiatric history (specify): History of sexual abuse: Y / N Other (specify):		

Test Results (where applicable):			
Oral glucose tolerance test:			
Glucose	HbA1c	HbG	
HDL	LDL	Triglyceride	
Upper gastrointestinal endoscopy:			
Overnight pulse oximetry:			
Lung Function Tests:			
Echocardiogram:			
CPX Test:			
VO2 max	AT	VEVCO2	
Postop Complications:			

1 Year Postoperatively:				
Weight (kg):	BMI:	eBMI:	% eBMI loss:	
Postop Drug History:				
DM medication stopped:	Yes	No	Reduced	N/A
Glucose	HbA1c		HbG	
BP medication stopped:	Yes	No	Reduced	N/A
BP /				

Appendix 2: Patient Information Sheet Version 2 (York Patients)

York Hospitals NHS
NHS Foundation Trust

Study Title:
Identification of Factors Predictive of Outcome following Bariatric Surgery

Dear [Insert patient's name],

You have recently been referred to York Hospital by your GP Dr [Insert GP's Name] for consideration for weight loss surgery. As a result of this referral I would like to invite you to take part in a research study. Before you decide whether or not you would like to take part in the study it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully. If you wish to talk to others about the study or would like to ask me anything then please feel free to contact me on the number given at the end of this letter. Please feel free to take as much time as you need to decide whether or not you wish to take part.

1- What is the purpose of the study?
As will be discussed when you come to your first outpatients appointment not all patients who have weight loss surgery lose as much weight as hoped. There are a variety of reasons why this may happen. The purpose of this research study is to look at our patients and see if there are any factors that seem to link those patients who do not lose as much weight as the others so that in the future we can ensure that this type of surgery only gets offered to those people who will benefit from it.

2- Why have I been invited to take part?
You have been invited to take part simply because you have been referred for this type of surgery. Everyone referred for weight loss surgery at York Hospital will receive an invitation to take part.

3- Do I have to take part?
No. Your participation in entirely voluntary and should you change your mind and withdraw at any stage then this is fine too – no reason for this needs to be given and your treatment and standard of care will not be affected at all.

4- What will happen to me if I take part?
The study has been designed to cause as little disruption as possible for the participants. When you come to the first outpatients clinic a series of measurements will be taken and a list of questions will be asked. If they are agreeable to it we would also like to measure the height and weight of your partner should they attend the clinic appointment with you. You will also be asked to fill in 5 questionnaires – these take between 1 minute and 5 minutes each. Aside from the measurements and questionnaires at the initial meeting the process for a participant of the study will be identical to someone not taking part in the study.

5- What will happen to me if I choose not to take part?
There are no negative consequences to not taking part in the study. If you choose not to be part of the study you will be treated in exactly the same manner as any other patient.

6- Are there any risks involved?
No. The only things required of participants of the study will be to complete the questionnaires, answer a few questions at interview and have the normal preoperative measurements and tests taken. There is no risk of injury during any of these processes.

7- What are the possible benefits of taking part?
The aim of this study is to help us to know which people we can help the most with weight loss surgery. You will be helping people in a similar position to you for years to come.

8- Will my taking part in this study be kept confidential?
Absolutely. None of the information taken as part of this study will contain your name - only a case-note number and this will only be accessible by the study team. All the information will be stored on an encrypted data-file with a password known only to the study team.

9- Who has reviewed the study?
All aspects of the study have been reviewed and approved by the Leeds Central Research Ethics Committee and the Research and Development departments at York Hospitals NHS Foundation Trust and Hull and East Yorkshire Hospitals. They are all responsible for ensuring that patient safety is never compromised and that all the ethical considerations are taken into account. In addition the University of York have analysed the study design to ensure that it is both safe and scientifically valid.

10- Who is organising and funding the research?
The study is being run by the bariatric (weight loss) surgery teams at York Hospital and Castle Hill Hospital and is being funded by the Hull-York Medical School.

11- What if there is a problem?
If you have a concern about any aspect of this study you should call the switchboard at either York Hospital on (01904) 631 313 or Castle Hill Hospital on (01482) 328 541. Ask to speak to me and I will do my best to satisfy your concerns. If you remain unhappy and wish to complain formally you can do this through the complaints department who are also contactable through the hospital switchboard.

Thank you for taking the time to read this letter. I sincerely hope that I have answered any questions that you may have over the nature of the study and hope to be able to include you in it in due course. Should you wish to speak to me about any aspect of this project prior to taking part then please call the switchboard and ask to speak to me.

Yours sincerely,

Mr Simon Adams
Clinical Research Fellow in General Surgery
York Hospital and Castle Hill Hospital

Version 2, 15/2/10

Appendix 3: Patient Consent Form (York Patients)

York Hospitals NHS
NHS Foundation Trust

Study Number: YOR-A01422
Patient Identification Number:

Title of Project: **Identification of Factors Predictive of Outcome following Bariatric Surgery**

Name of Principal Investigator: Mr Simon Adams

Please initial box

1. I confirm that I have read and understand the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the surgical departments in York Hospital, any monitor appointed by the Sponsor (University of York), from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

- ☐ Would you like to receive a copy of the results of this study after it finishes? (Yes/No)

Name of Patient Date Signature

Name of Person taking consent Date Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix 4: Patient Information Sheet Version 2 (Castle Hill Patients)

Study Title:
Identification of Factors Predictive of Outcome following Bariatric Surgery

Dear [Insert patient's name],

You have recently been referred to Castle Hill Hospital by your GP Dr [Insert GP's Name] for consideration for weight loss surgery. As a result of this referral I would like to invite you to take part in a research study. Before you decide whether or not you would like to take part in the study it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully. If you wish to talk to others about the study or would like to ask me anything then please feel free to contact me on the number given at the end of this letter. Please feel free to take as much time as you need to decide whether or not you wish to take part.

1) What is the purpose of the study?
As will be discussed when you come to your first outpatients appointment not all patients who have weight loss surgery lose as much weight as hoped. There are a variety of reasons why this may happen. The purpose of this research study is to look at our patients and see if there are any factors that seem to link those patients who do not lose as much weight as the others so that in the future we can ensure that this type of surgery only gets offered to those people who will benefit from it.

2) Why have I been invited to take part?
You have been invited to take part simply because you have been referred for this type of surgery. Everyone referred for weight loss surgery at Castle Hill Hospital will receive an invitation to take part.

3) Do I have to take part?
No. Your participation in entirely voluntary and should you change your mind and withdraw at any stage then this is fine too – no reason for this needs to be given and your treatment and standard of care will not be affected at all.

4) What will happen to me if I take part?
The study has been designed to cause as little disruption as possible for the participants. When you come to the first outpatients clinic a series of measurements will be taken and a list of questions will be asked. If they are agreeable to it we would also like to measure the height and weight of your partner should they attend the clinic appointment with you. You will also be asked to fill in 5 questionnaires – these take between 1 minute and 5 minutes each. Aside from the measurements and

questionnaires at the initial meeting the process for a participant of the study will be identical to someone not taking part in the study.

5) What will happen to me if I choose not to take part?
There are no negative consequences to not taking part in the study. If you choose not to be part of the study you will be treated in exactly the same manner as any other patient.

6) Are there any risks involved?
No. All that will be required will be to answer a few questions and have a few measurements taken.

7) What are the possible benefits of taking part?
The aim of this study is to help us to know which people we can help the most with weight loss surgery. You will be helping people in a similar position to you for years to come.

8) Will my taking part in this study be kept confidential?
Absolutely. None of the information taken as part of this study will contain your name - only a case-note number and this will only be accessible by the study team. All the information will be stored on an encrypted data-file with a password known only to the study team.

9) Who has reviewed the study?
All aspects of the study have been reviewed and approved by the Leeds Central Research Ethics Committee and the Research and Development departments at York Hospitals NHS Foundation Trust and Hull and East Yorkshire Hospitals. They are all responsible for ensuring that patient safety is never compromised and that all the ethical considerations are taken into account. In addition the University of York have analysed the study design to ensure that it is both safe and scientifically valid.

10) Who is organising and funding the research?
The study is being run by the bariatric (weight loss) surgery teams at York Hospital and Castle Hill Hospital and is being funded by the Hull-York Medical School.

11) What if there is a problem?
If you have a concern about any aspect of this study you should call the switchboard at either York Hospital on (01904) 631 313 or Castle Hill Hospital on (01482) 328 541. Ask to speak to me and I will do my best to satisfy your concerns. If you remain unhappy and wish to complain formally you can do this through the complaints department who are also contactable through the hospital switchboard.

Thank you for taking the time to read this letter. I sincerely hope that I have answered any questions that you may have over the nature of the study and hope to be able to include you in it in due course. Should you wish to speak to me about any aspect of this project prior to taking part then please call the switchboard and ask to speak to me.

Yours sincerely,

Mr Simon Adams
Clinical Research Fellow in General Surgery
York Hospital and Castle Hill Hospital

Version 2, 15/2/10

Appendix 5: Patient Consent Form (Castle Hill Patients)

Study Number: R0880
Patient Identification Number:

Title of Project: **Identification of Factors Predictive of Outcome following Bariatric Surgery**

Name of Principal Investigator: Mr Simon Adams

Please initial box

1. I confirm that I have read and understand the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the surgical departments in Castle Hill Hospital, any monitor appointed by the Sponsor (University of York), from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

- Would you like to receive a copy of the results of this study after it finishes? (Yes/No)

Name of Patient Date Signature

Name of Person taking consent Date Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix 6: Protocol for Patients Referred for RYGBP

Initial Consultation:

1) Measurement of
    a. Height
    b. Weight
    c. Blood pressure
2) Discussions exploring
    a. impact of obesity on
        i. lifestyle and health
        ii. patient's documented comorbidity
    b. methods of attempted weight loss in past
        i. their degree of success
    c. methods of surgical treatment and non-surgical treatment
        i. pros and cons of each
3) Specific to RYGBP discussion should include
    a. Irreversible nature of operation
    b. Gradual BWL over first 2 years
    c. Usually involves cholecystectomy
    d. Upper abdominal incision if open
    e. 4-7 day inpatient stay
    f. Importance of
        i. Understanding that surgery alone will not achieve the desired weight loss
        ii. Need for lifelong regular follow up
        iii. Need to be well informed prior to surgery
            1. Support group and British Obesity Surgery Patients Association (BOSPA) contact details to be provided
            2. Contact details to be provided of patient who has previously undergone surgery and is happy to be contacted
        iv. Commitment from individual
            1. Initial dietician consultation to
                a. optimise preoperative diet

b. discuss need for and nature of postoperative dietary and lifestyle modifications
c. discuss puree very low energy diet prior to laparoscopic RYGBP
d. discuss postoperative diet
    i. protein-rich puree for first 6 weeks
    ii. gradual progression in textures to normal consistency, small volume, high-protein/ low fat, well chewed meals (6 per day, 20-30 minutes each)
    iii. avoidance of drinks at mealtimes
    iv. avoidance of fizzy drinks, alcohol, fried foods, sweets, tough fibre

2. Failure to follow dietary and lifestyle modifications may result in ill-health and early eBWL plateau

g. 1% mortality
h. 10-20% major morbidity (thromboembolic, pneumonia, wound infection, bleeding, reoperation, anastomotic leakage, incisional hernia)
i. Minor morbidity (dumping syndrome, diarrhoea, hair loss (usually temporary), nutritional deficiencies)
j. Surgery to remove excess skin
    i. deemed cosmetic by PCTs and not currently supported
    ii. only necessary in 40-50% of patients

Second Consultation:

1) Measurement of
    a. Weight
    b. Blood pressure
2) Enquire about patient's efforts to become better informed
    a. Address any queries that may have arisen
3) If keen to proceed obtain baseline investigations
    a. Overnight pulse oximetry
    b. Oral glucose tolerance test
    c. Oesophagogastroduodenoscopy
    d. Laboratory tests
        i. Full blood count
        ii. Urea and electrolytes
        iii. Liver function tests, albumin, total protein
        iv. Parathyroid hormone, calcium, vitamin D
        v. Ferritin, vitamin B12, folate
        vi. Zinc, selenium, magnesium, copper
        vii. Free thyroxine, Thyroid stimulating hormone, cortisol
        viii. Luteinising hormone, follicle stimulating hormone
        ix. Testosterone, Sex hormone binding globulin
        x. Cholesterol
        xi. HbA1c, glucose
        xii. 24 hour urine collection for urinary corticosteroids
    e. Exercise tolerance test if aged over 50 and BW less than 150kg

Third Consultation:

1) Measurement of
    a. Weight
    b. Blood pressure
2) Review baseline investigations to exclude correctable cause of obesity
3) Address/ manage any comorbidities detected on baseline investigations
4) Discuss pros and cons/ risks of RYGBP again
5) List for surgery if still keen to proceed
    a. No sleep apnoea and BMI less than 50 kg/m^2 – level 0 or 1 bed
    b. Sleep apnoea not requiring continuous positive airway pressure (CPAP) – level 1 bed
    c. Sleep apnoea requiring home CPAP – level 1 or 2 bed
    d. Moderate to severe other comorbidity – level 2 bed
6) For the 10 days immediately prior to laparoscopic RYGBP patient is to take a very low energy diet

Preassessment:

1) Commence multivitamin and mineral supplements

Postoperative Inpatient:

1) Commence calcichew 1 tablet bd
2) Continue multivitamin and mineral supplements
3) Forceval 1 capsule od

Postoperative Outpatient:

1) At each appointment
    a. Assess BWL and symptoms (dysphagia, vomiting, diarrhoea, dumping)
    b. Assess wound
    c. Dietician review
    d. Laboratory tests
        i. Full blood count, urea and electrolytes, liver function tests
        ii. Zinc, selenium, magnesium, calcium
        iii. HbA1c, glucose (if T2DM present preoperatively)
    e. Additional laboratory tests if indicated
        i. Copper
        ii. Cortisol
        iii. Ferritin, folate
        iv. Follicle stimulating hormone, luteinising hormone, testosterone
        v. Vitamin D
    f. Supplement
        i. Zinc if below 8μmol/l
        ii. Selenium if below 0.6μmol/l
2) At 3 month, 6 month and annual appointments
    a. As above plus ferritin
        i. Supplement if below normal range
3) At annual appointments
    a. As above plus vitamin B12 and parathyroid hormone
        i. Supplement B12 every 3 months if below normal range

Appendix 7: Three Factor Eating Questionnaire R-18 (493, 494)

1 I deliberately take small helpings as a means of controlling my weight:

Definitely true Mostly True Mostly False Definitely False

2 I consciously hold back at meals in order not to gain weight:

Definitely true Mostly True Mostly False Definitely False

3 I do not eat some foods because they make me fat:

Definitely true Mostly True Mostly False Definitely False

4 How frequently do you avoid "stocking up" on tempting foods?

Almost never Seldom Usually Almost always

5 How likely are you to consciously eat less than you want?

Unlikely/ slightly Likely/ moderate Likely/ very likely

6 On a scale of 1 to 8 where 1 means no restraint in eating (eating whatever you want, whenever you want it) and 8 means total restraint (constantly limiting food intake and never "giving in"), what number would you give yourself?

1 2 3 4 5 6 7 8

7 When I smell a sizzling steak or a juicy piece of meat, I find it very difficult to keep from eating, even if I have just finished a meal:

Definitely true Mostly True Mostly False Definitely False

8 Sometimes when I start eating I just can't seem to stop:

Definitely true Mostly True Mostly False Definitely False

9 Being with someone who is eating often makes me hungry enough to eat also:

Definitely true Mostly True Mostly False Definitely False

10 When I see a real delicacy I often get so hungry that I have to eat right away:

Definitely true Mostly True Mostly False Definitely False

11 I get so hungry that my stomach often seems like a bottomless pit:

Definitely true Mostly True Mostly False Definitely False

12 I am always hungry so it is hard for me to stop eating before I finish the food on my plate:

Definitely true Mostly True Mostly False Definitely False

13 I am always hungry enough to eat at any time:

Definitely true Mostly True Mostly False Definitely False

14 How often do you feel hungry?

Only at mealtimes Sometimes between meals
Often between meals Almost always

15 Do you go on eating binges though you are not hungry?

Never Rarely Sometimes At least once a week

16 When I feel anxious I find myself eating:

Definitely true Mostly True Mostly False Definitely False

17 When I feel blue I often overeat:

Definitely true Mostly True Mostly False Definitely False

18 When I feel lonely I console myself by eating:

Definitely true Mostly True Mostly False Definitely False

Scoring of TFEQ (493, 494):

Sum of questions 1 – 6 = Cognitive restraint score

Sum of questions 7 - 15 = Uncontrolled Eating score

Sum of questions 16 - 18 = Emotional Eating score

Sum of all 3 components = overall score

Question		Definitely True	Mostly True	Mostly False	Definitely False
1	I deliberately take small helpings as a means of controlling my weight	4	3	2	1
2	I consciously hold back at meals in order not to gain weight	4	3	2	1
3	I do not eat some foods because they make me fat	4	3	2	1
4	How frequently do you avoid "stocking up" on tempting foods?	Almost Never 1 Seldom 2 Usually 3 Almost always 4			
5	How likely are you to consciously eat less than you want?	Unlikely 1 Slightly likely 2 Moderately likely 3 Very likely 4			
6	On a scale of 1 to 8 where 1 means no restraint in eating (eating whatever you want, whenever you want it) and 8 means total restraint (constantly limiting food intake and never "giving in"), what number would you give yourself?	1 or 2 = 1 3 or 4 = 2 5 or 6 = 3 7 or 8 = 4			

		Definitely True	Mostly True	Mostly False	Definitely False
7	When I smell a sizzling steak or a juicy piece of meat, I find it very difficult to keep from eating, even if I have just finished a meal	4	3	2	1
8	Sometimes when I start eating I just can't seem to stop	4	3	2	1
9	Being with someone who is eating often makes me hungry enough to eat also	4	3	2	1
10	When I see a real delicacy I often get so hungry that I have to eat right away	4	3	2	1
11	I get so hungry that my stomach often seems like a bottomless pit	4	3	2	1
12	I am always hungry so it is hard for me to stop eating before I finish the food on my plate	4	3	2	1
13	I am always hungry enough to eat at any time	4	3	2	1
14	How often do you feel hungry?	Only at mealtimes 1 Sometimes between meals 2 Often between meals 3 Almost always 4			
15	Do you go on eating binges though you are not hungry?	Never 1 Rarely 2 Sometimes 3 At least once per week 4			
16	When I feel anxious I find myself eating	4	3	2	1
17	When I feel blue I often overeat	4	3	2	1
18	When I feel lonely I console myself by eating	4	3	2	1

Appendix 8: Baecke Physical Activity Questionnaire (495)

Please circle the most appropriate response:

1) What is your main occupation?
2) At work I sit still:
   never seldom sometimes often always
3) At work I stand:
   never seldom sometimes often always
4) At work I walk:
   never seldom sometimes often always
5) At work I lift heavy loads:
   never seldom sometimes often always
6) After work I am tired:
   very often often sometimes seldom never
7) At work I sweat:
   very often often sometimes seldom never
8) In comparison with others of my own age I think my work is physically:
   much heavier heavier as heavy lighter much lighter
9) Do you play sport? Yes No
   If yes:
   a) Which sport do you play most frequently?
   b) How many hours a week?
   c) How many months a year?
   If you play a second sport:
   a) Which sport do you play most frequently?
   b) How many hours a week?
   c) How many months a year?
10) In comparison with others of my own age I think my physical activity during leisure time is:
   much more more the same less much less
11) During leisure time I sweat:
   very often often sometimes seldom never
12) During leisure time I play sport:
   never seldom sometimes often very often
13) During leisure time I watch television:
   never seldom sometimes often very often
14) During leisure time I walk:
   never seldom sometimes often very often
15) During leisure time I cycle:
   never seldom sometimes often very often
16) How many minutes do you walk and/ or cycle per day to and from work, school and shopping?
   <5 5-15 15-30 30-45 >45

BPAQ Scoring (495):

		Never	Seldom	Sometimes	Often	Very Often
1	What is your main occupation?	Low level activity (clerical, driving, shopkeeping, teaching, studying, housework, medical practice, occupations with university education) = 1 Moderate activity (factory, plumbing, carpentry, farming) = 3 High level activity (dock work, construction, sport) = 5				
2	At work I sit still	1	2	3	4	5
3	At work I stand	1	2	3	4	5
4	At work I walk	1	2	3	4	5
5	At work I lift heavy loads	1	2	3	4	5
6	After work I am tired	1	2	3	4	5
7	At work I sweat	1	2	3	4	5
8	In comparison with others of my own age I think my work is physically	Much lighter = 1 Lighter = 2 As heavy = 3 Heavier = 4 Much heavier = 5				
9	See below					

10	In comparison with others of my own age I think my physical activity during leisure time is	Much more = 5 More = 4 The same = 3 Less = 2 Much less = 1				
11	During leisure time I sweat	1	2	3	4	5
12	During leisure time I play sport	1	2	3	4	5
13	During leisure time I watch television	1	2	3	4	5
14	During leisure time I walk	1	2	3	4	5
15	During leisure time I cycle	1	2	3	4	5
16	How many minutes do you walk and/ or cycle per day to and from work, school and shopping?	<5 = 1 5 - 15 = 2 15 – 30 = 3 30 – 45 = 4 >45 = 5				

Please note that in questions 6, 7 and 11 the response items in the questionnaire are reversed compared to the other questions but the scoring for the equivalent responses is the same.

Question 9 is scored as follows:

- Do you play sport? Yes No
- If yes:

i) Which sport do you play most frequently?

Low level activity (billiards, sailing, bowling, golf etc) = 0.76

Moderate level activity (badminton, cycling, dancing, swimming, tennis etc) = 1.26

High level activity (boxing, basketball, football, rugby, rowing etc) = 1.76

ii) How many hours a week?

< 1hour = 0.5

1 - 3 hours = 1.5

4 – 6 hours = 2.5

7 – 9 hours = 3.5

> 9 hours = 4.5

iii) How many months a year?

< 1 = 0.04

1 – 3 = 0.17

4 – 6 = 0.42

7 – 9 = 0.67

> 9 = 0.92

If second sport played then repeat the above for the second sport

No = 0

Yes = Activity level score x hours per week score x months per year score for most frequent sport + Activity level score x hours per week score x months per year score for most second sport

If above figure is		
	0 then	= 1
	0.01≤ 4	= 2
	4 ≤ 8	= 3
	8 ≤ 12	= 4
	>12	= 5

Work index = (Q.1 + (6 – Q.2) + sum of Q.3 to Q.8) / 8

Sport index = (sum of Q.9 to Q.12) / 4

Leisure-time index = ((6 – Q.13) + sum of Q.14 to Q.16) / 4

Appendix 9: Obese Specific Quality of Life (496)

Please circle the most appropriate response

1) I have trouble squatting

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

2) I cannot sit down in a very low armchair

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

3) I walk as little as possible

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

4) I have to stop to catch my breath after walking several hundred metres

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

5) I have trouble climbing stairs

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

6) People say that I'm not very athletic

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

7) People often say that I'm not agile

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

8) I often lack energy

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

9) I don't move around very much

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

10) I feel I'm being attacked when people talk about my corpulence

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

11) I feel very ill at ease

Absolutely true Fairly True Neither True Nor False Fairly False Absolutely False

OSQoL Scoring (496):

Scores for individual items = score x coefficient

Absolutely True	+7.5
Fairly True	+3.5
Neither True nor False	+1.0
Fairly False	-1.0
Absolutely False	-4.5

Component	Question	Coefficient
Physical State	1. I have trouble squatting	15.58
	2. I cannot sit down in a very low armchair	17.19
	3. I walk as little as possible	15.72
	4. I have to stop to catch my breath after walking several hundred metres	16.7
	5. I have trouble climbing stairs	13.89
	6. People say that I'm not very athletic	12.35
	7. People often say that I'm not agile	15.66
Vitality, desire to do things	8. I often lack energy	49.41
	9. I don't move around very much	25.75
Relations with other people	10. I feel I'm being attacked when people talk about my corpulence	23.9
Psychological state	11. I feel very ill at ease	42.15

Physical State = sum of questions 1-7

Vitality = sum of questions 8 and 9

Relations with other people = question 10

Psychological state = question 11

Overall = sum of all 11 questions

Appendix 10: Ten Item Personality Inventory (497)

Here are a number of personality traits that may or may not apply to you. Please write a number next to each statement to indicate the extent to which you agree or disagree with that statement. You should rate the extent to which the pair of traits applies to you, even if one characteristic applies more strongly than the other.

1 - Disagree strongly
2 - Disagree moderately
3 - Disagree a little
4 - Neither agree nor disagree
5 - Agree a little
6 - Agree moderately
7 - Agree strongly

I see myself as:

1) Extraverted, enthusiastic ☐
2) Critical, quarrelsome ☐
3) Dependable, self-disciplined ☐
4) Anxious, easily upset ☐
5) Open to new experiences, complex ☐
6) Reserved, quiet ☐
7) Sympathetic, warm ☐
8) Disorganized, careless ☐
9) Calm, emotionally stable ☐
10) Conventional, uncreative ☐

Scoring of TIPI (497):

Q.1 + (8 – Q.6)	=	Extraversion
(8 – Q.2) + Q.7	=	Agreeableness
Q.3 + (8 – Q.8)	=	Conscientiousness
(8 – Q.4) + Q.9	=	Emotional Stability
Q.5 + (8 – Q.10)	=	Openness to Experiences
Total	=	Sum of all five domains

Appendix 11: University of Rhode Island Change Assessment (498):

1 = Strongly agree
2 = Agree
3 = Undecided
4 = Disagree
5 = Strongly Disagree

Circle the response that best describes how much you agree or disagree with each statement.

1. As far as I am concerned, I don't have any problem that needs changing. 1 2 3 4 5
2. I think I might be ready for some self-improvement. 1 2 3 4 5
3. I am doing something about the problems that have been bothering me. 1 2 3 4 5
4. It might be worthwhile to work on my problem. 1 2 3 4 5
5. I am not the one with a problem. It doesn't make much sense for me to be here. 1 2 3 4 5
6. It worries me that I might slip back on a problem I have already changed, so I am here to seek help. 1 2 3 4 5
7. I am finally doing some work on my problem. 1 2 3 4 5
8. I've been thinking that I might want to change something about myself. 1 2 3 4 5
9. I have been successful in working on my problem, but I'm not sure I can keep up the effort on my own. 1 2 3 4 5
10. At times my problem is difficult, but I'm working on it. 1 2 3 4 5
11. Being here is pretty much of a waste of time for me because the problem doesn't have to do with me. 1 2 3 4 5
12. I'm hoping this place will help me to better understand myself. 1 2 3 4 5
13. I guess I have faults, but there is nothing that I really need to change. 1 2 3 4 5
14. I am really working hard to change. 1 2 3 4 5
15. I have a problem and I really think I should work on it. 1 2 3 4 5
16. I'm not following through with what I had already changed as well as I had hoped, and I'm here to prevent a relapse of the problem. 1 2 3 4 5
17. Even though I'm not always successful in changing, I am at least working on my problem. 1 2 3 4 5
18. I thought once I had resolved the problem I would be free of it, but sometimes I still find myself struggling with it. 1 2 3 4 5
19. I wish I had more ideas on how to solve my problem. 1 2 3 4 5
20. I have started working on my problems, but I would like help. 1 2 3 4 5
21. Maybe this place will be able to help me. 1 2 3 4 5

22. I may need a boost right now to help me maintain the changes I've already made.
    1 2 3 4 5
23. I may be part of the problem, but I don't really think I am. 1 2 3 4 5
24. I hope that someone here will have some good advice for me. 1 2 3 4 5
25. Anyone can talk about changing; I'm actually doing something about it.
    1 2 3 4 5
26. All this talk about psychology is boring. Why can't people just forget about their problems? 1 2 3 4 5
27. I'm here to prevent myself from having a relapse of my problem. 1 2 3 4 5
28. It is frustrating, but I feel I might be having a recurrence of a problem I thought I had resolved. 1 2 3 4 5
29. I have worries but so does the next guy. Why spend time thinking about them? 1 2 3 4 5
30. I am actively working on my problem. 1 2 3 4 5
31. I would rather cope with my faults than try to change them. 1 2 3 4 5
32. After all I have done to try to change my problem, every now and again it comes back to haunt me. 1 2 3 4 5

Scoring of URICA (498, 518):

	Precontemplation	Contemplation	Action	Maintenance
Question Numbers	1	2	3	6
	5	8	7	16
	11	12	10	18
	13	15	14	22
	23	19	17	27
	26	21	25	28
	29	24	30	32
Total				
Divide by	7	7	7	7
Mean				

Readiness to change score = Mean contemplation score +
Mean action score +
Mean maintenance score –
Mean precontemplation score

Readiness to change score ≤ 8 classified as precontemplator

Readiness to change score 8 ≤ 11 classified as contemplator

Readiness to change score > 11 classified as action taker

Appendix 12: Search Strategies for Literature Reviews

Search Strategy for Chapter 3:

The following electronic sources were searched for potentially eligible randomised control trials and cohort studies:

MEDLINE (via Pubmed),

the Cochrane Database of Systematic Reviews (CDSR) and CENTRAL,

EMBASE

PsycINFO

CINAHL (Cumulative Index to Nursing and Allied Health Literature)

British Nursing Index

DARE (Database of Abstracts of Reviews of Effects) (all via NHS Evidence),

National Library of Guidelines,

NICE (National Institute of Clinical Excellence).

CPCI-S (Conference Proceedings Citation Index – Science) (via ISI Web of Knowledge)

The following journals were hand searched:

Obesity (formerly known as Obesity Research)

The International Journal of Obesity

Obesity Research and Clinical Practice

Surgery for Obesity and Related Diseases

Obesity Reviews

Obesity Surgery

New England Journal of Medicine

The Lancet

Annals of Surgery

Archives of Surgery

The following PubMed search strategy was used and adapted for use with other databases ([1] denotes MeSH index term):

#1 Gastroplasty[1] OR (gastric surgery) OR (gastric band*) OR (gastric bypass[1]) OR (lap-band) OR roux-en-y[1] OR (biliopancreatic diversion[1]) OR (biliopancreatic bypass[1]) OR gastro-gastrostomy[1] OR (restrictive surgery) OR (malabsorptive surgery) OR (bariatric surgery[1]) OR (jejunoileal bypass[1]) OR (jejuno-ileal bypass[1])

#2 obesity[1] OR obese[1] OR (weight loss[1]) OR (weight reduc*[1]) OR 'Obesity-morbid'/surgery

#3 #1 and #2

Search Strategy for Chapters 4 and 5:

No.	Database	Search term	Hits
1	MEDLINE	Exp BARIATRIC SURGERY/	9520
2	MEDLINE	Exp GASTROENTEROSTOMY/	6001
3	MEDLINE	BILIOPANCREATIC DIVERSION/	590
4	MEDLINE	ANASTOMOSIS, ROUX-EN-Y/	2323
5	MEDLINE	((bariatric surg*) OR (bariatric adj3 procedure*) OR (anti ADJ obes* ADJ surg*) OR (antiobes* ADJ surg*) OR (obes* ADJ surg*) OR (gastroplast*) OR (gastric ADJ bypass*) OR (gastric ADJ surg*) OR (Gastroileal ADJ Bypass*) OR (Gastro ADJ ileal Bypass*) OR (Gastrojejunostom*) OR (gastro ADJ gastrostom*) OR (gastrogastrostom*) OR (restrictive ADJ surg*) OR (restrictive* ADJ procedure*) OR (Gastroenterostom*) OR (Gastro ADJ enterostom*)).ti,ab	10744
6	MEDLINE	((Jejunoileal bypass*) OR (Jejuno ADJ ileal bypass*) OR (Jejunoileal ADJ surg*) OR (Jejuno ADJ ileal* ADJ surg*) OR (gastrointestinal* ADJ surg*) OR (gastrointestinal ADJ diversion*) OR (biliopancreatic ADJ diversion*) OR (bilio ADJ pancreatic diversion*) OR (biliopancreatic ADJ bypass*) OR (bilio ADJ pancreatic bypass*) OR (Ileojejunal Bypass*) OR (Ileojejunal Bypass*) OR (intestinal ADJ Bypass*)).ti,ab	3158
7	MEDLINE	((gastr* adj3 band*) OR (silicon ADJ	20487

No.	Database	Search term	Hits
		band*) OR (gastrectom*) OR (LAGB) OR (stomach* adj3 stapl*) OR (lap* ADJ band*) OR (lapband*) OR (malabsorptive ADJ procedure*) OR (malabsorptive ADJ surg*) OR (mason* ADJ procedure*) OR (roux ADJ en ADJ y) OR (duodenal ADJ switch*) OR (RYGB) OR (LRYGB) OR (RYGBP) OR (GBP) OR (VBG) OR (AGB) OR (LISG)).ti,ab	
8	MEDLINE	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	35383
9	MEDLINE	Exp OBESITY/	102265
10	MEDLINE	Exp OVERWEIGHT/	102440
11	MEDLINE	WEIGHT LOSS/	17273
12	MEDLINE	(Obes* OR overweight OR (over ADJ weight*) OR overeat* OR (over ADJ eat*) OR (weight ad3j loss) OR (losing adj3 weight*) OR (reduce* adj3 weight*) OR (weighing ADJ less) OR (decreas* adj3 weight*)).ti,ab	147571
13	MEDLINE	9 OR 10 OR 11 OR 12	182139
14	MEDLINE	8 AND 13	9339
15	MEDLINE	OBESITY/su [su=Surgery]	1955
16	MEDLINE	OBESITY, MORBID/su [su=Surgery]	4922
17	MEDLINE	14 OR 15 OR 16	10308
18	MEDLINE	Exp HYPERTENSION/	185421
19	MEDLINE	Exp BLOOD PRESSURE/	222922

No.	Database	Search term	Hits
20	MEDLINE	(Hyperten* OR (blood ADJ pressure*)).ti,ab	375510
21	MEDLINE	18 OR 19 OR 20	517705
22	MEDLINE	17 AND 21	797
23	MEDLINE	EPIDEMIOLOGIC STUDIES/	4830
24	MEDLINE	Exp CASE CONTROL STUDIES/	476102
25	MEDLINE	exp COHORT STUDIES/	776770
26	MEDLINE	CROSS-SECTIONAL STUDIES/	114543
30	MEDLINE	((Case* ADJ control*) OR (cohort* ADJ study) OR (cohort* ADJ studies) OR (cohort* ADJ analy*) OR (Follow ADJ up ADJ study) OR (follow ADJ up ADJ studies) OR (followup ADJ study) OR (followup ADJ studies) OR (observational ADJ study) OR (observational ADJ studies) OR Longitudinal OR Retrospective OR (Cross ADJ sectional)).ti,ab	512880
31	MEDLINE	23 OR 24 OR 25 OR 26 OR 30	1411020
32	MEDLINE	22 AND 31	356

Medline

Surgery

Exp bariatric surgery/ - should include (Gastric Bypass/ or Gastroplasty/ or Jejunoileal Bypass/ or Lipectomy/) or do separately
Exp Gastroenterostomy/
biliopancreatic diversion/
Anastomosis, Roux-en-Y/

(bariatric surg*) or (bariatric adj3 procedure*) or (anti adj obes* adj surg*) or (antiobes* adj surg*) or (obes* adj surg*) or (gastroplast*) or (gastric adj bypass*) or (gastric adj surg*) or (Gastroileal adj Bypass*) or (Gastro adj ileal Bypass*) or (Gastrojejunostom*) or (gastro adj gastrostom*) or (gastrogastrostom*) or (restrictive adj surg*) or (restrictive* adj procedure*) or (Gastroenterostom*) or (Gastro adj enterostom*)

(Jejunoileal bypass*) or (Jejuno adj ileal bypass*) or (Jejunoileal adj surg*) or (Jejuno adj ileal* adj surg*) or (gastrointestinal* adj surg*) or (gastrointestinal adj diversion*) or (biliopancreatic adj diversion*) or (bilio adj pancreatic diversion*) or (biliopancreatic adj bypass*) or (bilio adj pancreatic bypass*) or (Ileojejunal Bypass*) or (Ileojejunal Bypass*) or (intestinal adj Bypass*)

(gastr* adj3 band*) or (silicon adj band*) or (gastrectom*) or (LAGB) or (stomach* adj3 stapl*) or (lap* adj band*) or (lapband*) or (malabsorptive adj procedure*) or (malabsorptive adj surg*) or (mason* adj procedure*) or (roux adj en adj y) or (duodenal adj switch*) or (RYGB) or (LRYGB) or (RYGBP) or (GBP) or (VBG) or (AGB) or (LISG)

Weight loss

Exp Obesity/
Exp overweight/
Weight loss/
Obes* or overweight or (over adj weight*) or overeat* or (over adj eat*) or (weight ad3j loss) or (losing adj3 weight*) or (reduce* adj3 weight*) or (weighing adj less) or (decreas* adj3 weight*)

Hypertension

Exp hypertension/

Exp blood pressure/

Hyperten* or (blood adj pressure*)

Diabetes

Exp Diabetes Mellitus/

Exp glucose/

(Diabet* or glucose)

Embase

Exp bariatric surgery/

Gastroplasty/

Exp gastrectomy

Stomach bypass/

gastroenterostomy/

jejunoileal bypass/

Text words (as above)

Weight loss

Exp obesity

Weight reduction/

Text words (as above)

Hypertension

Exp Hypertension/

Exp blood pressure/

Text words (as above)

Diabetes

exp DIABETES MELLITUS/

exp DIABETES INSIPIDUS/

exp glucose/

exp glucose blood level/

Text words (as above)

PsycInfo

Surgery

Bariatric surgery/ (all other MeSH terms checked but no matches)

Text words

Weight loss

Obesity/ (narrower term of overweight)

Overweight/

Weight loss/

Weight control/

Text words

Blood pressure

Exp Blood pressure/

Blood pressure disorders/

Exp hypertension/ (includes essential hypertension)

Text words

Diabetes

Exp Diabetes/ (includes insipidus and mellitus)

Glucose/

Glucose metabolism/

Blood glucose/

Text words

CINAHL

Surgery

Exp bariatric surgery/

Exp Gastroenterostomy/

Anastomosis, Roux-en-Y/

Exp gastrectomy/

jejunoileal bypass/ (nil results at present)

Text words

Weight loss

Exp obesity/

Weight loss/

Weight control/

Text words

Hypertension

Exp hypertension/

Exp blood pressure/

Text words

Diabetes

Diabetes Insipidus/

Exp Diabetes Mellitus/

Glucose/

Blood glucose/

Text words

BNI

Surgery

Weight loss

Obesity/

Text words

Hypertension

Blood pressure/

Text words

Diabetes

Diabetes/

Text words

END

In addition the following journals were hand searched:

Obesity (formerly known as Obesity Research)

The International Journal of Obesity

Obesity Research and Clinical Practice

Surgery for Obesity and Related Diseases

Obesity Reviews

Obesity Surgery

New England Journal of Medicine

The Lancet

Annals of Surgery

Archives of Surgery

Search Strategy for Chapter 5:

Medline:

No.	Database	Search term	Hits
1	MEDLINE	BARIATRIC SURGERY/	1911
2	MEDLINE	GASTRIC BYPASS/	3396
3	MEDLINE	exp GASTROENTEROSTOMY/	6028
4	MEDLINE	ANASTOMOSIS, ROUX-EN-Y/	2329
5	MEDLINE	((bariatric ADJ surg*) OR (bariatric ADJ procedure*) OR (anti ADJ obes* ADJ surg*) OR (antiobes* ADJ surg*) OR (obes* adj3 surg*) OR (gastric ADJ bypass*) OR (gastric ADJ surg*) OR (gastroileal* ADJ bypass*) OR (gastro ADJ ileal* bypass*) OR (restrictive ADJ surg*) OR (restrictive* ADJ procedure*) OR (gastroenterostom*) OR (gastro ADJ enterostom*)).ti,ab	9871
6	MEDLINE	((gastrointestinal* ADJ surg*) OR (gastro ADJ intestinal* ADJ surg*) OR (intestinal ADJ bypass*) OR (stomach ADJ bypass*) OR (malabsorptive ADJ procedure*) OR (malabsorptive ADJ surg*) OR (roux ADJ en ADJ y) OR (RYGB) OR (LRYGB) OR (RYGBP) OR (GBP)).ti,ab	6687
7	MEDLINE	1 OR 2 OR 3 OR 4 OR 5 OR 6	18008
8	MEDLINE	Exp OBESITY/	103428
9	MEDLINE	Exp OVERWEIGHT/	103684
10	MEDLINE	WEIGHT LOSS/	17469
11	MEDLINE	(Obes* OR overweight OR (over ADJ weight*) OR overeat* OR (over ADJ eat*) OR (weight adj3 loss) OR weightloss OR (losing adj3 weight*) OR (reduc* adj3 weight*) OR (weigh* ADJ less) OR (decreas* adj3 weight*)).ti,ab	186960
12	MEDLINE	8 OR 9 OR 10 OR 11	215716

No.	Database	Search term	Hits
13	MEDLINE	7 AND 12	8052
14	MEDLINE	OBESITY/su [su=Surgery]	1980
15	MEDLINE	OBESITY, MORBID/su [su=Surgery]	4959
16	MEDLINE	13 OR 14 OR 15	10089
17	MEDLINE	Exp HYPERTENSION/	186300
18	MEDLINE	Exp BLOOD PRESSURE/	223899
19	MEDLINE	(Hyperten* OR (blood ADJ pressure*)).ti,ab	378190
20	MEDLINE	17 OR 18 OR 19	520785
21	MEDLINE	16 AND 20	806
22	MEDLINE	EPIDEMIOLOGIC STUDIES/	4882
23	MEDLINE	Exp CASE CONTROL STUDIES/	481682
24	MEDLINE	exp COHORT STUDIES/	783420
25	MEDLINE	CROSS-SECTIONAL STUDIES/	116485
26	MEDLINE	(((Case* ADJ control*) OR (cohort* ADJ study) OR (cohort* ADJ studies) OR (cohort* ADJ analy*) OR (Follow ADJ up ADJ study) OR (follow ADJ up ADJ studies) OR (followup ADJ study) OR (followup ADJ studies) OR (observational ADJ study) OR (observational ADJ studies) OR Longitudinal OR Retrospective OR (Cross ADJ sectional))).ti,ab	520220
27	MEDLINE	22 OR 23 OR 24 OR 25 OR 26	1426120
28	**MEDLINE**	**21 AND 27**	**353**

Embase

No.	Database	Search term	Hits
1	EMBASE	BARIATRIC SURGERY/	5578
2	EMBASE	STOMACH BYPASS/	4941
3	EMBASE	GASTROENTEROSTOMY/	2349
4	EMBASE	((bariatric ADJ surg*) OR (bariatric ADJ procedure*) OR (anti ADJ obes* ADJ surg*) OR (antiobes* ADJ surg*) OR (obes* adj3 surg*) OR (gastric ADJ bypass*) OR (gastric ADJ surg*) OR (gastroileal* ADJ bypass*) OR (gastro ADJ ileal* bypass*) OR (restrictive ADJ surg*) OR (restrictive* ADJ procedure*) OR (gastroenterostom*) OR (gastro ADJ enterostom*)).ti,ab	11526
5	EMBASE	((gastrointestinal* ADJ surg*) OR (gastro ADJ intestinal* ADJ surg*) OR (intestinal ADJ bypass*) OR (stomach ADJ bypass*) OR (malabsorptive ADJ procedure*) OR (malabsorptive ADJ surg*) OR (roux ADJ en ADJ y) OR (RYGB) OR (LRYGB) OR (RYGBP) OR (GBP)).ti,ab	7480
6	EMBASE	1 OR 2 OR 3 OR 4 OR 5	20493
7	EMBASE	Exp OBESITY/	172413
8	EMBASE	WEIGHT REDUCTION/	56135
9	EMBASE	(Obes* OR overweight OR (over ADJ weight*) OR overeat* OR (over ADJ eat*) OR (weight adj3 loss) OR weightloss OR (losing adj3 weight*) OR (reduc* adj3 weight*) OR (weigh* ADJ less) OR (decreas* adj3 weight*)).ti,ab	212788
10	EMBASE	7 OR 8 OR 9	285559
11	EMBASE	6 AND 10	10611
12	EMBASE	OBESITY/su [su=Surgery]	4559
13	EMBASE	MORBID OBESITY/su [su=Surgery]	4366
14	EMBASE	11 OR 12 OR 13	13045

No.	Database	Search term	Hits
15	EMBASE	exp HYPERTENSION/	337858
16	EMBASE	Exp BLOOD PRESSURE/	279763
17	EMBASE	exp BLOOD PRESSURE MEASUREMENT/	42877
18	EMBASE	(Hyperten* OR (blood ADJ pressure*)).ti,ab	431219
19	EMBASE	15 OR 16 OR 17 OR 18	668119
20	EMBASE	14 AND 19	1901
21	EMBASE	CLINICAL STUDY/	27789
22	EMBASE	CASE CONTROL STUDY/	48639
23	EMBASE	FAMILY STUDY/	8847
24	EMBASE	LONGITUDINAL STUDY/	41034
25	EMBASE	RETROSPECTIVE STUDY/	213301
26	EMBASE	PROSPECTIVE STUDY/	155576
27	EMBASE	COHORT ANALYSIS/	88195
28	EMBASE	CROSS-SECTIONAL STUDY/	45003
29	EMBASE	((Case* ADJ control*) OR (cohort* ADJ study) OR (cohort* ADJ studies) OR (cohort* ADJ analy*) OR (Follow ADJ up ADJ study) OR (follow ADJ up ADJ studies) OR (followup ADJ study) OR (followup ADJ studies) OR (observational ADJ study) OR (observational ADJ studies) OR (epidemiologic* ADJ study) OR (epidemiologic* ADJ studies) OR Longitudinal OR Retrospective OR (Cross ADJ sectional)).ti,ab	619801
30	EMBASE	21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29	952063
31	**EMBASE**	**20 AND 30**	**299**

BNI

No trial filter used as results were so few

No.	Database	Search term	Hits

No.	Database	Search term	Hits
1	BNI	((bariatric ADJ surg*) OR (bariatric ADJ procedure*) OR (anti ADJ obes* ADJ surg*) OR (antiobes* ADJ surg*) OR (obes* adj3 surg*) OR (gastric ADJ bypass*) OR (gastric ADJ surg*) OR (gastroileal* ADJ bypass*) OR (gastro ADJ ileal* bypass*) OR (restrictive ADJ surg*) OR (restrictive* ADJ procedure*) OR (gastroenterostom*) OR (gastro ADJ enterostom*)).ti,ab	85
2	BNI	((gastrointestinal* ADJ surg*) OR (gastro ADJ intestinal* ADJ surg*) OR (intestinal ADJ bypass*) OR (stomach ADJ bypass*) OR (malabsorptive ADJ procedure*) OR (malabsorptive ADJ surg*) OR (roux ADJ en ADJ y) OR (RYGB) OR (LRYGB) OR (RYGBP) OR (GBP)).ti,ab	29
3	BNI	1 OR 2	101
4	BNI	OBESITY/	1467
5	BNI	(Obes* OR overweight OR (over ADJ weight*) OR overeat* OR (over ADJ eat*) OR (weight adj3 loss) OR weightloss OR (losing adj3 weight*) OR (reduc* adj3 weight*) OR (weigh* ADJ less) OR (decreas* adj3 weight*)).ti,ab	1689
6	BNI	4 OR 5	1846
7	BNI	3 AND 6	79
8	BNI	BLOOD PRESSURE/	785
9	BNI	(Hyperten* OR (blood ADJ pressure*)).ti,ab	1490
10	BNI	8 OR 9	1599
11	**BNI**	**7 AND 10**	**1**

PsycInfo

No trial filter used as results were so few

1	PsycINFO	BARIATRIC SURGERY/	219
2	PsycINFO	((bariatric ADJ surg*) OR (bariatric ADJ procedure*) OR (anti ADJ obes* ADJ surg*) OR (antiobes* ADJ surg*) OR (obes* adj3	456

		surg*) OR (gastric ADJ bypass*) OR (gastric ADJ surg*) OR (gastroileal* ADJ bypass*) OR (gastro ADJ ileal* bypass*) OR (restrictive ADJ surg*) OR (restrictive* ADJ procedure*) OR (gastroenterostom*) OR (gastro ADJ enterostom*)).ti,ab	
3	PsycINFO	((gastrointestinal* ADJ surg*) OR (gastro ADJ intestinal* ADJ surg*) OR (intestinal ADJ bypass*) OR (malabsorptive ADJ procedure*) OR (malabsorptive ADJ surg*) OR (roux ADJ en ADJ y) OR (RYGB) OR (LRYGB) OR (RYGBP) OR (GBP)).ti,ab	124
4	PsycINFO	1 OR 2 OR 3	562
5	PsycINFO	OBESITY/	10155
6	PsycINFO	exp OVERWEIGHT/	10540
7	PsycINFO	WEIGHT LOSS/	1381
8	PsycINFO	WEIGHT CONTROL/	3040
9	PsycINFO	(Obes* OR overweight OR (over ADJ weight*) OR overeat* OR (over ADJ eat*) OR (weight adj3 loss) OR weightloss OR (losing adj3 weight*) OR (reduc* adj3 weight*) OR (weigh* ADJ less) OR (decreas* adj3 weight*)).ti,ab	22387
10	PsycINFO	5 OR 6 OR 7 OR 8 OR 9	23494
11	PsycINFO	4 AND 10	409
12	PsycINFO	Exp BLOOD PRESSURE/	4920
13	PsycINFO	BLOOD PRESSURE DISORDERS/	52
14	PsycINFO	Exp HYPERTENSION/	4162
15	PsycINFO	(Hyperten* OR (blood ADJ pressure*)).ti,ab	16932
16	PsycINFO	12 OR 13 OR 14 OR 15	17778
17	**PsycINFO**	**11 AND 16**	**20**

CINAHL

No.	Database	Search term	Hits
1	CINAHL	Exp BARIATRIC SURGERY/	1563
2	CINAHL	Exp GASTROENTEROSTOMY/	518

No.	Database	Search term	Hits
3	CINAHL	ANASTOMOSIS, ROUX-EN-Y/	11
4	CINAHL	((bariatric ADJ surg*) OR (bariatric ADJ procedure*) OR (anti ADJ obes* ADJ surg*) OR (antiobes* ADJ surg*) OR (obes* adj3 surg*) OR (gastric ADJ bypass*) OR (gastric ADJ surg*) OR (gastroileal* ADJ bypass*) OR (gastro ADJ ileal* bypass*) OR (restrictive ADJ surg*) OR (restrictive* ADJ procedure*) OR (gastroenterostom*) OR (gastro ADJ enterostom*)).ti,ab	1195
5	CINAHL	((gastrointestinal* ADJ surg*) OR (gastro ADJ intestinal* ADJ surg*) OR (intestinal ADJ bypass*) OR (malabsorptive ADJ procedure*) OR (malabsorptive ADJ surg*) OR (roux ADJ en ADJ y) OR (RYGB) OR (LRYGB) OR (RYGBP) OR (GBP)).ti,ab	285
6	CINAHL	1 OR 2 OR 3 OR 4 OR 5	2029
7	CINAHL	Exp OBESITY/	23065
8	CINAHL	WEIGHT LOSS/	6393
9	CINAHL	WEIGHT CONTROL/	3145
10	CINAHL	(Obes* OR overweight OR (over ADJ weight*) OR overeat* OR (over ADJ eat*) OR (weight adj3 loss) OR weightloss OR (losing adj3 weight*) OR (reduc* adj3 weight*) OR (weigh* ADJ less) OR (decreas* adj3 weight*)).ti,ab	25711
11	CINAHL	7 OR 8 OR 9 OR 10	38542
12	CINAHL	6 AND 11	1415
13	CINAHL	Exp HYPERTENSION/	22600
14	CINAHL	Exp BLOOD PRESSURE/	11936
15	CINAHL	(Hyperten* OR (blood ADJ pressure*)).ti,ab	30630
16	CINAHL	13 OR 14 OR 15	42985
17	CINAHL	12 AND 16	101
18	CINAHL	PROSPECTIVE STUDIES/	106897
19	CINAHL	Exp CASE CONTROL STUDIES/	22399

No.	Database	Search term	Hits
20	CINAHL	CORRELATIONAL STUDIES/	10941
21	CINAHL	NONCONCURRENT PROSPECTIVE STUDIES/	49
22	CINAHL	CROSS SECTIONAL STUDIES/	38196
23	CINAHL	((Case* ADJ control*) OR (cohort* ADJ study) OR (cohort* ADJ studies) OR (cohort* ADJ analy*) OR (Follow ADJ up ADJ study) OR (follow ADJ up ADJ studies) OR (followup ADJ study) OR (followup ADJ studies) OR (observational ADJ study) OR (observational ADJ studies) OR Longitudinal OR Retrospective OR (Cross ADJ sectional) OR (epidemiologic* ADJ study) OR (epidemiologic* ADJ studies)).ti,ab	83054
24	CINAHL	18 OR 19 OR 20 OR 21 OR 22 OR 23	200516
25	**CINAHL**	**17 AND 24**	**20**

Appendix 13: SPSS Analysis Syntaxes

1) Generalisability SG vs EG:

i)

```
GET
FILE='C:\Desktop\Work\Thesis\12 Month Data.sav'.
DATASET NAME DataSet1 WINDOW=FRONT.
CROSSTABS
  /TABLES=geneticr ethnicit primaryr tfeq18 bpaq osqol_overall tipi
urica_score alcohol smoke social pattern comorb BY studygrp
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

ii)

```
USE ALL.
COMPUTE filter_$=(studygrp = 1).
VARIABLE LABELS filter_$ 'studygrp = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
FREQUENCIES VARIABLES=geneticr ethnicit primaryr tfeq18 bpaq
osqol_overall tipi urica_score alcohol smoke social pattern comorb
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN
  /ORDER=ANALYSIS.
```

iii)

```
USE ALL.
COMPUTE filter_$=(studygrp = 0).
VARIABLE LABELS filter_$ 'studygrp = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
FREQUENCIES VARIABLES=geneticr ethnicit primaryr tfeq18 bpaq
osqol_overall tipi urica_score alcohol smoke social pattern comorb
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN
  /ORDER=ANALYSIS
```

iv)

```
USE ALL.
COMPUTE filter_$=(studygrp = 0).
VARIABLE LABELS filter_$ 'studygrp = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
FREQUENCIES VARIABLES=secondar cogrestr uncontro emotiona
workinde sportind leisuret physical_state vitality relations psychological
extravert agreeable conscience emotstab optoexp py_hx ihd bp osa
copdasth diabetes pcos psych sexabuse otherpmh
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN
  /ORDER=ANALYSIS.
```

v) USE ALL.
COMPUTE filter_$=(studygrp = 1).
VARIABLE LABELS filter_$ 'studygrp = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
FREQUENCIES VARIABLES=secondar cogrestr uncontro emotiona workinde sportind leisuret physical_state vitality relations psychological extravert agreeable conscience emotstab optoexp py_hx ihd bp osa copdasth diabetes pcos psych sexabuse otherpmh
/STATISTICS=STDDEV MINIMUM MAXIMUM MEAN
/ORDER=ANALYSIS.

vi) FILTER OFF.
USE ALL.
EXECUTE.
CROSSTABS
/TABLES=secondar cogrestr uncontro emotiona workinde sportind leisuret physical_state vitality relations psychological extravert agreeable conscience emotstab optoexp py_hx ihd bp osa copdasth diabetes pcos psych sexabuse otherpmh BY studygrp
/FORMAT=AVALUE TABLES
/STATISTICS=CHISQ
/CELLS=COUNT
/COUNT ROUND CELL.

vii)

```
USE ALL.
COMPUTE filter_$=(sex = 0).
VARIABLE LABELS filter_$ 'sex = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
CROSSTABS
  /TABLES= pcos BY studygrp
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

viii)

```
GET
  FILE='C:\Users\Simon\Desktop\Work\Thesis\12 Month Data.sav'.
DATASET NAME DataSet1 WINDOW=FRONT.
CROSSTABS
  /TABLES=ihd bp osa copdasth diabetes pcos psych sexabuse otherpmh
BY studygrp
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

ix) USE ALL.

```
COMPUTE filter_$=(sex = 0).
VARIABLE LABELS filter_$ 'sex = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
CROSSTABS
  /TABLES=pcos BY studygrp
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

2) Comparison SG vs EG:

i)
```
GET
FILE='C:\Users\Simon\Desktop\Work\Thesis\12 Month Data.sav'.
DATASET NAME DataSet1 WINDOW=FRONT.
CROSSTABS
  /TABLES=sex decade bmigrp BY studygrp
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

ii)
```
CROSSTABS
  /TABLES=sex BY studygrp
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL
  /BARCHART.
```

iii)
```
USE ALL.
COMPUTE filter_$=(studygrp = 0).
VARIABLE LABELS filter_$ 'studygrp = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
FREQUENCIES VARIABLES=bmi age
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN
  /HISTOGRAM NORMAL
  /ORDER=ANALYSIS.
```

iv)

```
USE ALL.
COMPUTE filter_$=(studygrp = 1).
VARIABLE LABELS filter_$ 'studygrp = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
FREQUENCIES VARIABLES=bmi age
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN
  /HISTOGRAM NORMAL
  /ORDER=ANALYSIS.
```

v)

```
* Chart Builder.
GGRAPH
  /GRAPHDATASET NAME="graphdataset" VARIABLES=bmigrp
studygrp MISSING=LISTWISE REPORTMISSING=NO
  /GRAPHSPEC SOURCE=INLINE.
BEGIN GPL
  SOURCE: s=userSource(id("graphdataset"))
  DATA: bmigrp=col(source(s), name("bmigrp"))
  DATA: studygrp=col(source(s), name("studygrp"), unit.category())
  GUIDE: axis(dim(1), label("BMI Group"))
  GUIDE: axis(dim(2), label("Frequency"))
  GUIDE: axis(dim(3), label("optype = 1 & fuavail = 1 & fu_duration >=
250 (FILTER)"), opposite())
  SCALE: cat(dim(3), include("0", "1"))
  ELEMENT:
interval(position(summary.count(bin.rect(bmigrp*1*studygrp))),
shape.interior(shape.square))
END GPL.
```

vi) * Chart Builder.

```
GGRAPH
  /GRAPHDATASET NAME="graphdataset" VARIABLES=age
studygrp MISSING=LISTWISE REPORTMISSING=NO
  /GRAPHSPEC SOURCE=INLINE.
BEGIN GPL
  SOURCE: s=userSource(id("graphdataset"))
  DATA: age=col(source(s), name("age"))
  DATA: studygrp=col(source(s), name("studygrp"), unit.category())
  GUIDE: axis(dim(1), label("Age"))
  GUIDE: axis(dim(2), label("Frequency"))
  GUIDE: axis(dim(3), label("optype = 1 & fuavail = 1 & fu_duration >=
250 (FILTER)"), opposite())
  SCALE: cat(dim(3), include("0", "1"))
  ELEMENT:
interval(position(summary.count(bin.rect(age*1*studygrp))),
shape.interior(shape.square))
END GPL.
```

3) SG Outcomes and Analysis:

i)

```
GET
  FILE='C:\Users\Simon\Desktop\Work\Thesis\12 Month Data.sav'.
DATASET NAME DataSet1 WINDOW=FRONT.
USE ALL.
COMPUTE filter_$=(studygrp = 1).
VARIABLE LABELS filter_$ 'studygrp = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
* Chart Builder.
GGRAPH
  /GRAPHDATASET NAME="graphdataset"
VARIABLES=oneyr_pctebmiloss MISSING=LISTWISE
REPORTMISSING=NO
  /GRAPHSPEC SOURCE=INLINE.
BEGIN GPL
  SOURCE: s=userSource(id("graphdataset"))
  DATA: oneyr_pctebmiloss=col(source(s), name("oneyr_pctebmiloss"))
  GUIDE: axis(dim(1), label("1Yr % eBMI Loss"))
  GUIDE: axis(dim(2), label("Frequency"))
  ELEMENT:
interval(position(summary.count(bin.rect(oneyr_pctebmiloss))),
shape.interior(shape.square))
END GPL.
```

ii)

```
FREQUENCIES VARIABLES=oneyr_pctebmiloss
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN
  /ORDER=ANALYSIS.
```

iii) REGRESSION
/MISSING LISTWISE
/STATISTICS COEFF OUTS R ANOVA
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT oneyr_pctebmiloss
/METHOD=ENTER geneticr ethnicit primaryr tfeq18 bpaq osqol_overall tipi urica_score alcohol smoke social fullpart comorb.

iv) REGRESSION
/MISSING LISTWISE
/STATISTICS COEFF OUTS R ANOVA
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT oneyr_pctebmiloss
/METHOD=STEPWISE geneticr ethnicit primaryr tfeq18 bpaq osqol_overall tipi urica_score alcohol smoke social fullpart comorb

v) REGRESSION
/MISSING LISTWISE
/STATISTICS COEFF OUTS R ANOVA
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT oneyr_pctebmiloss
/METHOD=STEPWISE secondar cogrestr uncontro emotiona workinde sportind leisuret physical_state vitality relations psychological extravert agreeable conscience emotstab optoexp ihd bp osa copdasth diabetes pcos psych sexabuse otherpmh.

vi) * Chart Builder.

```
GGRAPH
  /GRAPHDATASET NAME="graphdataset" VARIABLES=sportind
oneyr_pctebmiloss MISSING=LISTWISE REPORTMISSING=NO
  /GRAPHSPEC SOURCE=INLINE.
BEGIN GPL
  SOURCE: s=userSource(id("graphdataset"))
  DATA: sportind=col(source(s), name("sportind"))
  DATA: oneyr_pctebmiloss=col(source(s), name("oneyr_pctebmiloss"))
  GUIDE: axis(dim(1), label("Sport Index"))
  GUIDE: axis(dim(2), label("1Yr % eBMI Loss"))
  ELEMENT: point(position(sportind*oneyr_pctebmiloss))
END GPL.
```

vii) LOGISTIC REGRESSION VARIABLES oneyr_goodresult

```
  /METHOD=ENTER geneticr ethnicit primaryr tfeq18 bpaq
osqol_overall tipi urica_score alcohol smoke social pattern comorb
  /CONTRAST (ethnicit)=Indicator
  /CONTRAST (primaryr)=Indicator
  /CONTRAST (smoke)=Indicator
  /CONTRAST (social)=Indicator
  /CONTRAST (pattern)=Indicator
  /CONTRAST (comorb)=Indicator
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20) CUT(.5).
```

viii) LOGISTIC REGRESSION VARIABLES oneyr_goodresult

```
  /METHOD=ENTER urica_score smoke extravert conscience emotstab
optoexp agreeable tipi
  /CONTRAST (smoke)=Indicator
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20) CUT(.5).
```

ix) GET

FILE='C:\Users\Simon\Desktop\Work\Thesis\12 Month Data.sav'.

DATASET NAME DataSet1 WINDOW=FRONT.

USE ALL.

FILTER BY studygrp.

EXECUTE.

LOGISTIC REGRESSION VARIABLES oneyr_goodresult

/METHOD=ENTER secondar cogrestr uncontro emotiona workinde sportind leisuret physical_state vitality relations psychological extravert agreeable conscience emotstab optoexp ihd bp osa copdasth diabetes psych sexabuse otherpmh pcos

/CONTRAST (secondar)=Indicator

/CONTRAST (ihd)=Indicator

/CONTRAST (bp)=Indicator

/CONTRAST (osa)=Indicator

/CONTRAST (copdasth)=Indicator

/CONTRAST (diabetes)=Indicator

/CONTRAST (psych)=Indicator

/CONTRAST (sexabuse)=Indicator

/CONTRAST (otherpmh)=Indicator

/CONTRAST (pcos)=Indicator

/CRITERIA=PIN(.05) POUT(.10) ITERATE(20) CUT(.5).

4) Secondary Outcome Analysis

i)
```
FREQUENCIES VARIABLES=diabetes dm_meds dmmedsto
  /ORDER=ANALYSIS.
```

ii)
```
USE ALL.
COMPUTE filter_$=(studygrp = 1 & diabetes = 0).
VARIABLE LABELS filter_$ 'studygrp = 1 & diabetes = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
FREQUENCIES VARIABLES=preop_hba1c
  /STATISTICS=STDDEV MEAN
  /ORDER=ANALYSIS.
```

iii)
```
USE ALL.
COMPUTE filter_$=(studygrp = 1 & diabetes = 1 & dm_meds = 0).
VARIABLE LABELS filter_$ 'studygrp = 1 & diabetes = 1 & dm_meds
= 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
FREQUENCIES VARIABLES=preop_hba1c
  /STATISTICS=STDDEV MEAN
  /ORDER=ANALYSIS.
```

iv)

```
USE ALL.
COMPUTE filter_$=(studygrp = 1 & diabetes = 1 & dm_meds = 1 &
dmmedsto = 1).
VARIABLE LABELS filter_$ 'studygrp = 1 & diabetes = 1 & dm_meds
= 1 & dmmedsto = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
T-TEST PAIRS=preop_hba1c WITH postop_hba1c (PAIRED)
  /CRITERIA=CI(.9500)
  /MISSING=ANALYSIS.
```

v)

```
USE ALL.
COMPUTE filter_$=(studygrp = 1 & diabetes = 1 & dm_meds = 1 &
dmmedsto = 2).
VARIABLE LABELS filter_$ 'studygrp = 1 & diabetes = 1 & dm_meds
= 1 & dmmedsto = 2 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
T-TEST PAIRS=preop_hba1c WITH postop_hba1c (PAIRED)
  /CRITERIA=CI(.9500)
  /MISSING=ANALYSIS.
```

vi) USE ALL.

```
COMPUTE filter_$=(studygrp = 1 & bp = 0).
VARIABLE LABELS filter_$ 'studygrp = 1 & bp = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
T-TEST PAIRS=preop_sbp preop_dbp WITH postop_sbp postop_dbp
(PAIRED)
  /CRITERIA=CI(.9500)
  /MISSING=ANALYSIS.
```

vii) USE ALL.

```
COMPUTE filter_$=(studygrp = 1 & bp_meds = 1).
VARIABLE LABELS filter_$ 'studygrp = 1 & bp_meds = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
CROSSTABS
  /TABLES=bp_meds BY bpmedsto
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

viii) USE ALL.

```
COMPUTE filter_$=(studygrp = 1 & bp_meds = 1 & bpmedsto = 1).
VARIABLE LABELS filter_$ 'studygrp = 1 & bp_meds = 1 & bpmedsto
= 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
T-TEST PAIRS=preop_sbp preop_dbp WITH postop_sbp postop_dbp
(PAIRED)
  /CRITERIA=CI(.9500)
  /MISSING=ANALYSIS.
```

ix) USE ALL.

```
COMPUTE filter_$=(studygrp = 1 & bp_meds = 1 & bpmedsto = 2).
VARIABLE LABELS filter_$ 'studygrp = 1 & bp_meds = 1 & bpmedsto
= 2 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
T-TEST PAIRS=preop_sbp preop_dbp WITH postop_sbp postop_dbp
(PAIRED)
  /CRITERIA=CI(.9500)
  /MISSING=ANALYSIS.
```

x)

```
USE ALL.
COMPUTE filter_$=(studygrp = 1 & dm_meds = 1).
VARIABLE LABELS filter_$ 'studygrp = 1 & dm_meds = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
LOGISTIC REGRESSION VARIABLES dmmedsto
  /METHOD=ENTER geneticr ethnicit primaryr tfeq18 bpaq
osqol_overall tipi urica_score alcohol smoke social pattern comorb
  /CONTRAST (ethnicit)=Indicator
  /CONTRAST (primaryr)=Indicator
  /CONTRAST (social)=Indicator
  /CONTRAST (pattern)=Indicator
  /CONTRAST (smoke)=Indicator
  /CONTRAST (comorb)=Indicator
 /CRITERIA=PIN(.05) POUT(.10) ITERATE(20) CUT(.5).
```

xi)

```
USE ALL.
COMPUTE filter_$=(studygrp = 1 & bp_meds = 1).
VARIABLE LABELS filter_$ 'studygrp = 1 & bp_meds = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
LOGISTIC REGRESSION VARIABLES bpmedsto
  /METHOD=ENTER geneticr ethnicit primaryr tfeq18 bpaq
osqol_overall tipi urica_score alcohol smoke social pattern comorb
  /CONTRAST (ethnicit)=Indicator
  /CONTRAST (primaryr)=Indicator
  /CONTRAST (social)=Indicator
  /CONTRAST (pattern)=Indicator
  /CONTRAST (smoke)=Indicator
  /CONTRAST (comorb)=Indicator
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20) CUT(.5).
```

5) Discussion and Conclusions

i)

```
GET
  FILE='C:\Users\Simon\Desktop\Work\Thesis\12 Month Data.sav'.
DATASET NAME DataSet1 WINDOW=FRONT.
* Chart Builder.
GGRAPH
  /GRAPHDATASET NAME="graphdataset" VARIABLES=workinde
MISSING=LISTWISE REPORTMISSING=NO
  /GRAPHSPEC SOURCE=INLINE.
BEGIN GPL
  SOURCE: s=userSource(id("graphdataset"))
  DATA: workinde=col(source(s), name("workinde"))
  GUIDE: axis(dim(1), label("Work Index"))
  GUIDE: axis(dim(2), label("Frequency"))
  ELEMENT: interval(position(summary.count(bin.rect(workinde))),
shape.interior(shape.square))
END GPL.
```

ii) * Chart Builder.

```
GGRAPH
  /GRAPHDATASET NAME="graphdataset" VARIABLES=social
oneyr_pctebmiloss MISSING=LISTWISE REPORTMISSING=NO
  /GRAPHSPEC SOURCE=INLINE.
BEGIN GPL
  SOURCE: s=userSource(id("graphdataset"))
  DATA: social=col(source(s), name("social"), unit.category())
  DATA: oneyr_pctebmiloss=col(source(s), name("oneyr_pctebmiloss"))
  DATA: id=col(source(s), name("$CASENUM"), unit.category())
  GUIDE: axis(dim(1), label("Social Class"))
  GUIDE: axis(dim(2), label("1Yr % eBMI Loss"))
  SCALE: cat(dim(1), include("1", "2", "3", "4", "5", "6", "7", "8", "9"))
  SCALE: linear(dim(2), include(0))
  ELEMENT:
schema(position(bin.quantile.letter(social*oneyr_pctebmiloss)), label(id))
END GPL.
```

Appendix 14: Publications Yielded from this Study at Time of Submission

- Clinical Prediction Rules
  Adams ST, Leveson SH
  British Medical Journal 2012 January 16th; 344:d8312.
  doi: 10.1136/bmj.d8312

- Obesity-related Hypertension and its Remission Following Gastric Bypass Surgery – A Review of the Mechanisms and Predictive Factors
  Adams ST, Salhab M, Hussain ZI, Miller GV, Leveson SH
  Blood Pressure 2012 Dec 18, Jun;22(3):131-7
  doi:10.3109/08037051.2012.749570

- Roux-en-Y Gastric Bypass for Morbid Obesity: What Are the Predictors of Weight Loss?
  Adams ST, Salhab M, Hussain ZI, Miller GV, Leveson SH
  Postgraduate Medical Journal 2013, Jul;89(1053):411-6
  doi: 10.1136/postgradmedj-2012-131310

- Preoperatively Determinable Factors Predictive of Diabetes Mellitus Remission following Roux-en-Y Gastric Bypass – A Review of the Literature
  Adams ST, Salhab M, Hussain ZI, Miller GV, Leveson SH
  Acta Diabetologica 2013, Aug;50(4):475-8
  doi:10.1007/s00592-013-0453-2

BMJ

BMJ 2012;344:d8312 doi: 10.1136/bmj.d8312 (Published 16 January 2012)

RESEARCH METHODS & REPORTING

Clinical prediction rules

Clinical prediction rules are mathematical tools that are intended to guide clinicians in their everyday decision making. The popularity of such rules has increased greatly over the past few years. This article outlines the concepts underlying their development and the pros and cons of their use

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In many ways much of the art of medicine boils down to playing the percentages and predicting outcomes. For example, when clinicians take a history from a patient they ask the questions that they think are the most likely to provide them with the information they need to make a diagnosis. They might then order the tests that they think are the most likely to support or refute their various differential diagnoses. With each new piece of the puzzle some hypotheses will become more likely and others less likely. At the end of the process the clinician will decide which treatment is likely to result in the most favourable outcome for the patient, based on the information they have obtained.

Given that the above process is the underlying principle of clinical practice, and bearing in mind the ever increasing time constraints imposed on people, it is unsurprising that a great deal of work has been done to help clinicians and patients make decisions. This work is referred to by many names: prediction rules, probability assessments, prediction models, decision rules, risk scores, etc. All describe the combination of multiple predictors, such as patient characteristics and investigation results, to estimate the probability of a certain outcome or to identify which intervention is most likely to be effective.[1 2] Predictors are identified by "data mining"—the process of selecting, exploring, and modelling large amounts of data in order to discover unknown patterns or relations.[3]

Ideally, a reliable predictive factor or model would combine both a high sensitivity with a high specificity.[4 5] In other words it would correctly identify as high a proportion as possible of the patients fated to have the outcome in question (sensitivity) while excluding those who will not have the outcome (specificity).[6] In the table⇓ sensitivity can be defined as A÷(A+C) and specificity as D÷(B+D).

A good predictive factor is not the same as a strong risk factor.[4] The positive predictive value of a predictive factor or model refers to its accuracy in terms of the proportion of patients correctly predicted to have the outcome in question (A÷(A+B) in the table⇓).[7] A risk factor can be identified by calculating the relative risk (or odds ratio) of an outcome in patients with the factor in question compared with patients without it.[4] If, however, the factor identified or the outcome being used is uncommon, it is of little clinical use as a predictive factor.[4 7]

A good predictive factor or model shows a good fit between the probabilities calculated from the model and the outcomes actually observed, while also accurately discriminating between patients with and without the outcome.[4 5] For example, if all patients with a measured observation of ≥0.5 die and all patients with the measured observation <0.5 survive then the observed factor is a perfect predictor of survival.

Unfortunately, as a general rule sensitivity and specificity are mutually exclusive—as one rises the other falls. Since both are important to the development of predictive models receiver-operating characteristic (ROC) curves are used to visualise the trade-off between the two and express the overall accuracy of the model (fig 1⇓).[4 8 9] Sensitivity (true positive) is plotted on the y axis and 1−specificity (false positive) is plotted on the x axis.[4 9] The closer a point is to the top left of the graph then the higher the area under the curve and the more accurate or useful a predictive factor can be said to be.[4 8 9] Conversely a plot in the 45 degree diagonal (denoting an area under the curve of 50%) indicates a test no more accurate than chance.[4 8 9] Where the limits of acceptability are set is arbitrary and depends on several factors such as the severity of the outcome and the potential negative consequences of the test.[4 9]

Establishing a clinical prediction rule

The establishment of a prediction model in clinical practice requires four distinct phases:

Development—Identification of predictors from an observational study

Validation—Testing of the rule in a separate population to see if it remains reliable

Impact analysis—Measurement of the usefulness of the rule in the clinical setting in terms of cost-benefit, patient satisfaction, time/resource allocation, etc

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Implementation—Widespread acceptance and adoption of the rule in clinical practice.

For a prediction rule to gain popularity each of the first three steps needs to be satisfactorily completed before the fourth stage.[1] Validation in a suitably powered cohort study or controlled trial is particularly important because there is no guarantee that a predictor will be accurate outside the original data set.[1 2] Indeed validation usually shows a reduction in accuracy compared to that in the original study.[1 10-12] Reliability is essentially the reproducibility of a measurement—that is, if the same test were applied under the same circumstances how similar the results would be.

Despite the long running controversy concerning their usefulness and application the popularity of clinical prediction rules has been shown to be greater now than ever.[1 13 14] A Medline search by Toll and colleagues in 2008 showed that the number of papers discussing prediction rules has more than doubled in recent years (6744 papers in 1995 versus 15 662 in 2005).[1] Most publications, however, concern the development of new rules, with few articles describing validation and almost none confirming their clinical impact.[1] There are several possible reasons why validation and impact analysis are so often overlooked. Perhaps the most important are that neither validity nor reliability can be exactly quantified and that establishing validity requires investigators to consider several different aspects (face validity, content validity, construct validity, criterion validity, etc).[15 16]

Advantages and disadvantages of prediction rules

When appropriately developed and validated, prediction models have inherent advantages over human clinical decision making. Firstly, the statistical models can accommodate many more factors than the human brain is capable of taking into consideration.[17] Secondly, if given identical data a statistical model will always give the same result whereas human clinical judgment has been shown to result in both inconsistency and disparity, especially with less experienced clinicians.[17 18] Finally, and perhaps most importantly, several prediction models have been shown to be more accurate than clinical judgment alone.[14 17-21] So why are such models not used more readily in every practice?

Liao and Mark proposed in 2003 that resistance to adopting prediction models may reflect tacit acknowledgment that clinicians do not know how to take advantage of such tools.[17] They also suggested that such tools may not be thought user friendly and may not take into account the continual, dynamic way in which humans gather clinical information.[17] Their final reason for low implementation of clinical prediction rules is the sheer number of models available.[17] If multiple prediction rules exist for the same problem identifying the best one is difficult. Not only is it potentially very time consuming but differences in the methods used in the studies on which they are based may make reliable comparison impossible.[11 22] Part of the reason for the large number of prediction rules may be the wide variety of ways in which such tools can be developed.

Types of prediction model

In 2006 Grobman and Stamilio described five main methods used to develop clinical prediction models: scoring systems derived from univariate analysis, prediction models based on multivariate analysis, nomograms, artificial neural networks, and decision trees.

Scoring systems derived from univariate analysis

Factors shown to be significantly related to the outcome in observational studies are allocated a score or "weight." The cumulative final score of all the risk factors present in a patient is used as an indicator of the likelihood of the outcome occurring.[4] Well known examples of this type of prediction model include the Alvarado score for acute appendicitis and the modified Glasgow score for acute pancreatitis.[23 24] These models are simple to devise and use but their accuracy is affected by the potential inclusion of non-independent risk factors and the arbitrary manner in which factors are weighted.[4]

Prediction models based on multivariate analysis

These are developed in a similar manner to the above scoring systems except that the analysis of the results from the observational study is more refined and therefore less likely to include any non-independent factors. The models typically use logistic regression analysis, which has the added advantage of expressing the relation between the predictive factors and the outcome in the form of odds ratios (the probability of an outcome occurring versus the probability that it will not).[4] These are relatively easy to interpret and can also be used to assign weights in a less arbitrary fashion than in univariate models.[4 25] Nevertheless, multivariate analysis techniques are not completely reliable in eliminating bias from interaction of independent variables.[4] Models using logistic regression are often well suited to being represented as a nomogram (see below).[3]

Nomograms

Nomograms are graphical calculating devices that represent mathematical relations or laws and allow the user to rapidly calculate complicated formulas to a practical precision (fig 2⇓).[26] Nomograms may be as simple as the markings on a thermometer or more complex, such as the Siggaard-Andersen chart used to diagnose acid-base blood disorders.[27] The mathematics and statistics used to develop a nomogram can be equally simplistic or intricate.[4] The advantage of nomograms is that the final prediction tool created is generally comparatively simple to use and in some cases more accurate than other prediction models for the same clinical problem.[4 28] Other nomograms in common clinical use include those used to predict the likelihood of a patient having prostate cancer from their clinical examination and prostate specific antigen levels and those used to predict the peak expiratory flow rate of asthmatic patients based on their age and height.[29 30]

Prediction using artificial neural networks

Artificial neural networks are mathematical or computational models based on the operation of biological neural networks.[31] In biology, a nerve cell (or neuron) will receive input from numerous other nerve cells. It will then process all of the input it receives and either send off an action potential or not. Because these nerve cells are all interconnected they are referred to as networks. Artificial neural networks function along similar lines: multiple sources of information (input) are fed into the software program, which interprets it and produces a dichotomous output (fig 3⇓). The main advantage of neural networks is that they can "learn" mathematical relations between a series of input variables and the corresponding output.[32-35] This is achieved by inputting a set of data containing both the input data (the predictor variables) as well as the outcomes.[32 33] With each new

data set entered the neural network is able to adjust the internal weights of the various pieces of input data and calculate the probability of a specific outcome.[32]

Neural networks require little formal statistical training to develop and can implicitly detect complex non-linear relations between independent and dependent variables as well as all possible interactions between predictor variables.[32 33] However, they have a limited ability to explicitly identify possible causal relations, they are hard to use at the bedside, and they require greater computational resources than other prediction models.[32 33] They are also prone to "overfitting"—when too many data sets are used in training the network causing it to effectively memorise the noise (irrelevant data) and reducing its accuracy.[32 33] A final drawback to neural networks is that the development model is empirical and because it is a new technique methodological problems remain.[32] In a direct comparison between neural networks and logistic regression models Tu and colleagues concluded that neural networks were better for predicting outcomes but that logistic regression was preferable when looking for possible causal relations between independent and dependent variables or when trying to understand the effect of predictor variables on an outcome.[32]

Decision trees (CART analysis)

Classification and regression tree (CART) analysis uses non-parametric tests to evaluate data and progressively divide it into subgroups based on the predictive independent variables.[4] The variables and discriminatory values used and the order in which the splitting occurs are produced by the underlying mathematical algorithm and are calculated to maximise the resulting predictive accuracy.[4] CART analysis produces "decision trees," which are generally easily understood and consequently translate well into everyday clinical practice (fig 4⇓). By following the arrows indicated by the answers to each of the questions in the boxes clinicians will be directed to the predicted outcome for the patient. Examples of CARTs used in clinical practice include those to predict large oesophageal varices in cirrhotic patients and to predict the likelihood of hospital admission in patients with asthma.[36 37] However, the CART model of prediction can be significantly less accurate than other models.[28 38] This may be because the "leaves" on the trees contain too little data to be able to predict outcomes reliably.[3]

Conclusion

Each of the five main models has advantages and disadvantages, and no single model of prediction has been clearly shown to be superior to the others in all applications. As pressure on their time increases, doctors will need to become familiar with decision making tools and the statistical principles underlying them.

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Competing interests: All authors have completed the unified disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the past three years; and no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Table

Table 1| **Tabular representation of predicted versus actual outcomes of a predictive model**

	Actual outcome	
Predicted outcome	**Positive**	**Negative**
Positive	A (true positive)	B (false positive)
Negative	C (false negative)	D (true negative)

Figures

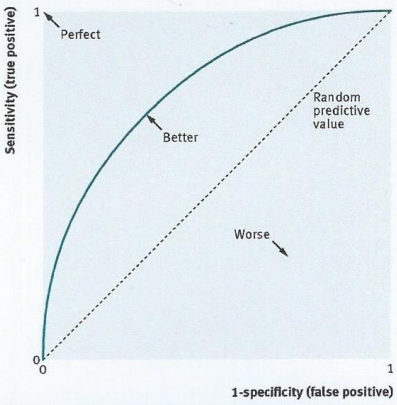

Fig 1 Receiver-operating characteristic (ROC) curve

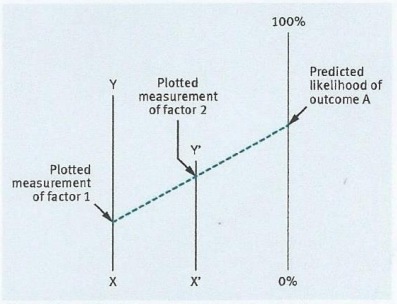

Fig 2 Simplified representation of a basic nomogram

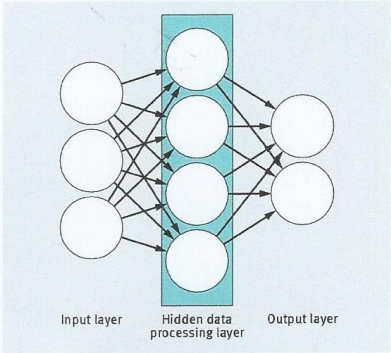

Fig 3 Schematic representation of an artificial neural network. The first column (input layer) represents a piece of data that can be put in to the neural network programme. The circles in the second column (hidden layer) represent the neural network programme assigned weight or numerical significance of each piece of data entered in the input layer. The final column (output layer) represents the dichotomous predicted outcome for the information entered

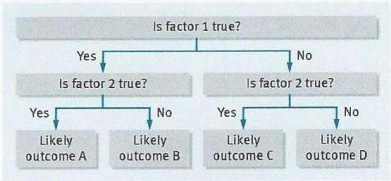

Fig 4 Simplified representation of a basic decision tree

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REVIEW ARTICLE

Obesity-related hypertension and its remission following gastric bypass surgery – A review of the mechanisms and predictive factors

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Abstract

It is well established that hypertension and obesity appear to be associated. The exact mechanism by which they are linked is unclear and remains a topic of a great deal of research. Current NICE guidelines recommend that patients with a BMI in excess of 35 kg/m^2 should be considered for bariatric surgery if they have a concomitant obesity-associated condition, of which hypertension is one. The commonest bariatric procedure in the UK is the Roux-en-Y gastric bypass, which has been shown to result in long-standing remission of hypertension in up to 93% of patients. This paper summarizes the existing literature on the main theories as to how obesity leads to hypertension as well as the literature concerning the effects of gastric bypass surgery on hypertension.

Key Words: *obesity, hypertension, gastric bypass*

Introduction

The adverse health consequences of obesity are many and varied – almost every system in the body can be affected (1,2). A systematic review in 2010 suggested hazard ratios of between 1.1 and 5.1 for the development of cardiometabolic morbidity [type 2 diabetes mellitus (DM), hypertension, ischaemic heart disease and cerebrovascular disease] in adulthood amongst overweight or obese children as compared with children of normal weight (3). Attempts to quantify the exact reduction in life expectancy imposed by obesity have varied; however, the generally accepted figure of 7 years would imply that obesity has as great an impact as lifelong smoking (3–5).

The relationship between hypertension and adiposity has been well established in numerous studies over the past few decades across a variety of ethnicities and weight ranges (6–9). In 1987, Garrison et al. (8) estimated that up to 78% of cases of hypertension in men and 64% of cases in women may be directly attributable to patients either being overweight or obese (8,10). The connection between the two has been further clarified by such studies as Jones et al. (11), who showed that there was a linear relationship between blood pressure (BP) and body mass index (BMI) – for every BMI increase of 1 kg/m^2 in normal weight individuals the diastolic BP rose by 0.89 mmHg, whereas in overweight individuals it increased by 1 mmHg. Subsequent studies have shown a similar correlation (7). Having said all this, it is worth remembering that despite the increased prevalence of hypertension in the obese population, not all obese patients are hypertensive and not all hypertensive patients have a raised BMI (6,12). Although even modest BMI increases and decreases can result in corresponding changes in BP, in both the normal weight and overweight/obese populations, there is still considerable inter-individual variability (6,12–14).

Pathophysiology of obesity-related hypertension

Exactly how obesity leads to hypertension is not fully understood; however, several overlapping theories have been proposed. Central to these theories is the concept that the adipose tissue of overweight or obese individuals is "dysfunctional" (10,15). This means that the tissue differs from normal adipose tissue by showing increased levels of adipocyte hypertrophy and macrophage infiltration and an

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altered secretory function of the adipocyte-released hormones (adipokines) (10,15). It is primarily this altered adipokine secretion component that underpins the hypotheses explaining the aetiology of obesity-associated hypertension.

Sympathetic nervous system dysfunction

The main proposed mechanism stems from the proven link between elevated body fat levels and overstimulation of the sympathetic nervous system (SNS) (6,12,16–18). Activation of the SNS may induce hypertension by inducing peripheral vasoconstriction, impairing the urinary excretion of sodium and water and by stimulation of the renin–angiotensin–aldosterone system (RAAS) (10). It should be borne in mind, however, that SNS activity may occur regionally or systemically and much of the literature on this topic is based on the erroneous assumption that systemic markers of SNS activity, such as those of skeletal muscle, are equal in effect to the SNS activity specific to those organs controlling BP, most notably the kidneys (12,19,20). It has been suggested that obesity may not in fact result in systemic SNS hyperactivity but may instead result in a more selective SNS activation process – for example, skeletal muscle and renal SNS activity may be increased in obese patients, but cardiac SNS activity may be reduced due to baroreflex inhibition with the increased heart rate seen instead being a consequence of reduced parasympathetic activity (12,20–22). Those studies conducted since the development of more site-specific neurochemical and neurophysiological techniques have been pivotal in enhancing our understanding of the pathophysiology of obesity-related hypertension (19).

As a result of these site-specific techniques, there is now good evidence clarifying the link between body fat levels and SNS activity (19,20). Several studies have shown that obese humans demonstrate up to twice the levels of post-ganglionic muscle SNS activity compared with non-obese subjects (13,17,19,20,23–25). It has also been shown that ethnicity plays a role in the relationship between SNS activity, obesity and BP (10,26). An example of this finding would be Weyer et al. (26), who found that muscle SNS activity positively related to body fat percentage in Caucasians in whom obesity and hypertension are both widely prevalent but not Pima Indians in whom levels of obesity are high but levels of hypertension are low. In addition, Alvarez et al. (23) showed that SNS activity is more closely related to levels of intra-abdominal (visceral) than total fat mass or abdominal subcutaneous fat independently of total body fat (6,12,19,23,27). This in turn would explain why such patients have also been found to have a greater association with hypertension and cardiovascular disease (6,12,23,27). The broad mechanisms linking obesity and SNS activity have been described in several review articles and are briefly outlined below.

Hyperleptinaemia

Leptin secretion by adipocytes occurs proportionately to fat mass and its levels are therefore raised in obese subjects (12,28–30). It acts primarily on receptors in the hypothalamus resulting in decreased appetite and increased peripheral thermogenesis (6,12,16). Epidemiological evidence, studies of patients with congenital leptin deficiency and animal studies have also suggested a role for leptin in renal SNS activation and increased BP in the long-term if not acutely (12,16,31–33). It appears to exert its central effects on the SNS by acting on receptors, which form parts of other CNS systems such as the melanocortin receptors in the anterior pituitary gland (12,34). It is thought that obese subjects may be selectively resistant to leptin's effects on weight control but not to its influence on renal SNS activity; however, the exact mechanism for this has yet to be proven (16,35).

Hypoadiponectinaemia

High molecular weight adiponectin has been shown to have a significant cardio-protective effect in terms of lowering BP and reducing the incidence of atheromatous plaque formation (12,36). In contrast to most adipocyte-secreted hormones, however, its levels in obesity are reduced (36–38). Exactly how adiponectin reduces BP is not known but studies on rats have shown a dose-dependent reduction in renal SNS function when given either intravenously or intraventricularly (12,39). In addition, adiponectin has been shown to stimulate the actions of endothelial nitric oxide synthase thus inducing a reduction in vascular tone and smooth muscle proliferation (10,36,40,41). The elevated levels of free fatty acid and tumour necrosis factor-α seen in obesity are thought to impair nitric oxide synthase function and thus contribute to increased BP in a parallel fashion to the effects of hypoadiponectinaemia (10,42).

Hypoghrelinaemia

Ghrelin produced in the stomach and pancreas increases during fasting and appears to trigger the sensation of hunger. Rodent studies have suggested that it also counteracts the effects of leptin on melanocortin receptors thus inhibiting renal and systemic SNS activity (43,44). Ghrelin has also been shown to increase endothelial nitric oxide production thus resulting in reduced vascular tone (45). Low ghrelin levels would therefore result in less central sympatho-inhibition and less systemic vasodilatation with a consequential increase in systemic BP.

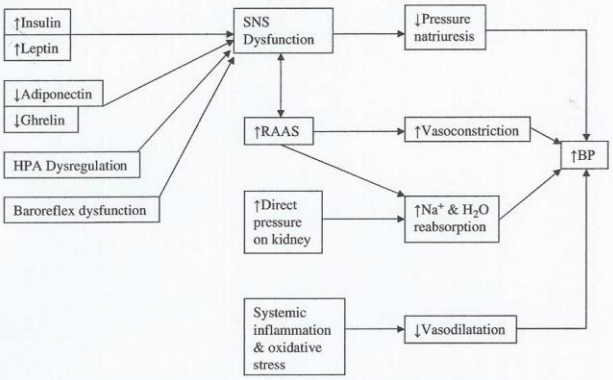

Figure 1. Mechanisms by which obesity induces hypertension.

Insulin resistance/hyperinsulinaemia

Although the evidence implicating insulin resistance in obesity-related hypertension is fairly weak, it has been postulated that the two may be indirectly linked by the effects of the former in terms of arterial intimal damage or chronic lipid metabolism dysfunction (6). The main arguments against hyperinsulinaemia playing a role in hypertension in the acute or subacute settings are that studies of BP in animals in whom insulin has been infused intravenously or directly into the brain do not show a concomitant sustained rise in BP (6,12,46,47). Equally patients on therapeutic intravenous insulin drips or with proven insulinomas do not show a tendency towards hypertension (48,49).

Baroreflex dysfunction

Baroreflex function has been shown to be impaired in obesity, particularly visceral obesity, and there is evidence that this phenomenon is another action attributable to leptin (21,27,50–54). However, since the baroreceptor reflex acts primarily to maintain acute BP stability, there remains some doubt as to the degree of influence this mechanism may exert on the BP of obese individuals in the long-term (6,12).

Hypothalamic–pituitary axis (HPA) dysregulation

It has been suggested that simultaneous activation of the SNS and HPA may play a role in the development of obesity-related hypertension (6,55). Evidence to support this hypothesis came in 2001 when Grassi et al. (56) demonstrated that prolonged glucocorticoid administration resulted in SNS inhibition in obese but not normal weight subjects concluding that the HPA may affect SNS function in several ways (6,56). Since these early findings, it has been suggested that a variety of other metabolites, for example reactive oxygen species, may act on HPA pathways to induce sympatho-excitation with subsequent increases in BP (57).

Renin–angiotensin–aldosterone system dysfunction

The second major hypothesis linking obesity to hypertension, related to the overstimulation of the SNS, is the concomitant increased activity in obesity of the RAAS, which brings about rises in BP via a variety of hormones primarily by directly augmenting renal sodium and water reabsorption and systemic vascular tone (10,58,59). One of the major RAAS components, angiotensin II, has also been shown indirectly to increase BP acutely through central excitation of the SNS and baroreceptor reflexes (6,60–62). Paradoxically though, the effect on SNS function appears to reverse on chronic exposure (63). Although the RAAS hormones are mainly secreted from organs other than adipose tissue, nearly all of them are elevated in obesity and reduce in concentration following bodyweight loss (BWL) (10,58,64–69). It is clear that with the elevated levels

Resolution of hypertension	
Positive correlation	Negative correlation
↓age	↓weight loss Afro-Caribbean ethnicity ↑Duration of hypertension Concomitant diabetes mellitus

Figure 2. Factors associated with the resolution of hypertension following Roux-en-Y gastric bypass (RYGBP).

of the RAAS hormones in obesity, a direct effect on BP could occur; however, the role of the RAAS on the SNS remains uncertain (10).

Systemic inflammation and oxidative stress

The third major hypothesis linking hypertension to overweight and obesity centres on the well established association between increased adiposity and elevated levels of systemic inflammation and oxidative stress (10,70,71). It is thought that the common link between the two is that several of the pro-inflammatory cytokines and acute phase reactants have been shown to impair the vasodilatory function of vascular mediators such as nitric oxide (10,70,72,73). In addition, the direct pressure effect of the adipose tissue on the kidneys is thought to elevate BP by encouraging sodium and water retention (64,74). Both pathways would provide plausible explanations as to why visceral obesity is particularly associated with hypertension as patients with predominantly elevated levels of intra-abdominal fat have been shown to have increased levels of systemic inflammatory markers, oxidative stress and intra-abdominal pressure as compared with those with predominantly subcutaneous fat (71,75–77).

Roux-en-Y gastric bypass (RYGBP) and hypertension resolution

In comparison with the number of papers investigating its effects on BMI and DM there is a relative dearth of data concerning the influence that RYGBP may have on BP. The largest series of RYGBP on hypertensive patients was reported in 2003 by Sugerman et al. (78), who investigated 1025 patients of whom 521 were hypertensive (defined as systolic BP $\geq$ 150 mmHg, diastolic BP $\geq$ 90 mmHg and/or the use of antihypertensive medication). At 1–2 years post-RYGBP, hypertension had resolved in 69% of these patients [excess BWL (eBWL) 66 $\pm$ 18%, 91% follow-up rate] with this figure falling to 66% at 5–7 years (eBWL 59 $\pm$ 24%, 50% follow-up rate) and 51% at 10–12 years (eBWL 52 $\pm$ 25%, 37% follow-up rate) (78). The risk factors for non-resolution of hypertension were increased age, lower eBWL and African-American ethnicity ($p < 0.001$, $p < 0.001$ and $p < 0.02$, respectively) (78). The, perhaps predictable, finding that hypertension is more likely to resolve or improve if more weight is lost echoes those of smaller similar studies (79,80). Interestingly, it has been shown that in the majority of post-RYGBP patients not only does BP tend towards normal levels but also that the natural circadian rhythm of BP is generally restored – a phenomenon that is typically impaired in obesity (81).

Hinojosa et al. (82) reported a mean eBWL of 66% in a cohort of 95 patients and a 46% complete resolution rate at 12 months post-RYGBP with a further 19% of patients showing some improvement in their hypertension. Analogous to the findings of several studies looking at factors associated with DM resolution Hinojosa et al. (82) found that the duration since diagnosis of hypertension was an independent risk factor for resolution with the complete resolution group having a mean duration of 53 months vs 95 months in the non-resolution group ($p = 0.001$).

The only other published factor associated with successful resolution of hypertension following RYGBP is that of DM status. Carbonell et al. (83) reported on a cohort of 3193 patients of whom 655 (20%) also had DM. Although the paper does not state how many of the 3193 patients were hypertensive preoperatively, it does conclude that those subjects without concomitant DM were significantly more likely to experience resolution of their hypertension than those with both conditions (74.4% vs 63.5%, $p < 0.0001$) (83).

Given that there are a variety of mechanisms by which obesity is thought to induce hypertension, it is perhaps not unreasonable to think that there may be a variety of mechanisms by which post-bariatric surgery BWL may induce its remission. It used to be thought that BWL itself was the key factor driving the return to normotension; however, a time-course analysis published in 2009 showed that improvements in BP occur well before any appreciable BWL (84,85). Ahmed et al. (84) found that in their cohort of 100 patients the systolic and diastolic BPs reduced by 9 and 7 mmHg respectively at 1 week post-RYGBP. These measurements fell by a further 6 and 2 mmHg, respectively, with an overall 88% hypertension resolution rate over the remaining 12-month follow-up period, suggesting that BWL itself is not the key determinant of BP normalization following RYGBP (84). It is likely that the early improvements in BP, if not the long-term improvements, are the result of a hormonal mechanism (84). One possible explanation was proposed by Sledzinski et al. in 2010 (86) who reported a 40% increased in serum nitric oxide levels 6 months post-vertical banded gastroplasty, although clearly the differences in the nature of this procedure and the RYGBP make it difficult to draw confident parallels. Improvements in endothelial vasomotor function and aortic elasticity following RYGBP have been described in the literature; however, the significance of these findings with regard to long-term BP control is not clear (87,88).

Conclusion

Whilst the link between obesity and hypertension is well established, there continues to be some controversy regarding the exact nature of the association. That BWL, whether surgical or non-surgical, effects a change towards normotension appears to be equally

well accepted but again the mechanisms by which it does so remain elusive. In comparison with BWL and DM remission, few attempts appear to have been made to identify factors predictive of hypertension remission. Given the disease burden, this would seem to be a worthy area for future research.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Roux-en-Y gastric bypass for morbid obesity: what are the preoperative predictors of weight loss?

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ABSTRACT

Obesity has become an increasingly important health problem over the past 30 years. Presently around a quarter of the UK adult population are obese and this figure is set to increase further in the coming decades. The health consequences of obesity on multiple body systems have been well established as has the financial cost of the condition to both the individuals affected as well as to society as a whole. Bariatric surgery has been shown to be the only long term effective solution in terms of sustained weight loss and comorbidity resolution. The commonest bariatric procedure in the UK is the Roux-en-y gastric bypass which consistently results in the loss of 70%-80% of excess bodyweight. Results however are variable and in order to optimise resource allocation and avoid exposing patients unlikely to benefit from surgery to its inherent risks, much research has been done to try to identify those patients most likely to obtain a good result. The only factor which has been subjected to meta-analysis is that of preoperative weight loss which shows a positive association with postoperative weight loss following bypass surgery. Although the remaining data are not based on level 1 evidence those other preoperatively identifiable factors which are associated with an improved outcome include Caucasian or Hispanic ethnicity, higher educational status, non-shift-work working patterns, female gender and divorced or single marital status. Similarly increased levels of preoperative physical activity and an absence of binge eating behaviour are consistent with a favourable result whereas increased age, smoking and other socioeconomic factors have not been shown to have a significant impact. Conversely diabetes mellitus seems to have a slight negative correlation with postoperative weight loss; however, a history of sexual abuse or psychiatric illness has not been shown to have a lasting influence.

INTRODUCTION

The levels of obesity in the UK have trebled over the past 30 years with recent estimates showing 23% of men and 25% of women to be obese.[1] This figure is set to increase over the next few decades with the estimated prevalence of obesity in the UK projected to reach 60% of male subjects and 50% of female subjects by 2050.[2] Numerous studies have demonstrated the deleterious effects of obesity both in terms of the health of the individual and of the financial cost to society.[3–5] Bariatric surgery has been shown to be the most effective treatment for obesity in the long term with the gold standard procedure being the Roux-en-y gastric bypass (RYGBP) which consistently shows excess bodyweight loss (eBWL) of 70%–80%.[3 6 7] It should be noted however that bariatric surgery can be defined as having been a success or failure in several different ways. While the most obvious and easily measureable parameter of success would be weight loss, which in the case of the RYGBP should result in upwards of 60% loss of excess weight, some clinicians would argue that the resolution of comorbidities is of greater benefit to the patient. Others, however, would argue that functional or psychological improvement or increased life expectancy should be the goal of bariatric intervention. In addition to being clinically effective in achieving long term weight loss and curing or reducing many of the obesity-related comorbidities, bariatric surgery has also been shown to be a financially viable option with the cost being recouped within 2–4 years of surgery.[4 8–13] Despite these favourable attributes the outcomes of bariatric surgery remain highly procedure and surgeon specific.[5] A successful outcome is also highly dependent on the patients' compliance with alterations in their eating habits and levels of physical activity.[14–16] Consequently, a great deal of research has been done to try to identify those patients preoperatively who are most likely to benefit from surgery in order to optimise resource allocation, avoid exposing patients unlikely to benefit from surgery to its inherent risks and in order to manage patients' expectations. In this paper, we review those factors suggested to be preoperative determinants of outcome following RYGBP.

PATIENT DEMOGRAPHIC FACTORS

Age

One of the more contentious issues of recent years has been the ongoing debate about the appropriateness of operating for morbid obesity in the elderly. In 2010, Willkomm *et al*[17] conducted the largest single institution study comparing the outcomes of laparoscopic RYGBP in patients over 65 years of age with those under 65 years of age. Although the operative risk profile was expectedly greater in the older age group the outcomes in terms of complication rates, mortality, inpatient stay, 30-day readmission rates and eBWL at 12 and 24 months were similar between the two groups.[17] Such findings have been supported in several similar studies but are at odds with those of Flum *et al* and Livingston and Langert who independently concluded that mortality was significantly greater in the over 65 age group and whose papers led to a reduction in the operative rate among this population.[17–23] It has been suggested that these discrepancies may be the result of methodological differences between the latter studies when compared with the

To cite: Adams ST, Salhab M, Hussain ZI, *et al*. *Postgrad Med J* Published Online First: [*please include* Day Month Year] doi:10.1136/postgradmedj-2012-131310

former.[17] Thus far, research has concentrated on the effects advanced age has on the safety of RYGBP with little attention being paid to its use as a predictor of weight loss. Published data would appear conflicting with some studies finding that younger age predicted greater weight loss and others finding the opposite.[17 24] As yet, no meta-analyses have been performed to quantify the usefulness of age as a predictor of weight loss following RYGBP.

Ethnicity

Several studies have looked at the subject of ethnicity to see whether racial background has an influence on the degree of eBWL following RYGBP. All but one of the studies that have compared Caucasians with people of Afro-Caribbean descent have found a significantly greater degree of eBWL in the investigated Caucasian populations.[25–31] However, no significant difference has been shown to exist between people of Hispanic descent as compared with Caucasians.[32 33] Why these racial differences exist and whether they exist across all ethnic minorities and all types of bariatric intervention is not currently known. Similarly, the degree to which ethnicity can be used as a prognostic indicator is also currently unquantified but there remains a strong suggestion that certain races do experience a more favourable outcome following RYGBP than others.

Socioeconomic status

Given that a large proportion of the bariatric surgery performed worldwide occurs in the USA it is perhaps unsurprising that much interest has been shown in the effect that socioeconomic status, particularly medical insurance status, may have on outcomes following such procedures. Most of these studies however have focused on bariatric surgery as a whole and have used outcome measures such as complication rates, length of stay and mortality.[22 34 35] In general, the literature suggests that Medicare (publicly funded) patients tend to be younger and to have a greater disease burden than privately insured patients.[23 36] Specific to eBWL following RYGBP there are only a handful of noteworthy papers. The earliest, by Martin *et al*[37] in 1991, found that publicly funded patients experienced no significant difference compared with privately insured patients but that this group did experience a substantially higher rate of medical and psychiatric complications. Interestingly, Martin also observed that 45% of the publicly funded patients were able to find employment postoperatively allowing them to reduce their levels of financial support.[37] More recent studies have supported Martin's finding regarding eBWL post-RYGBP.[14 38] Other socioeconomic factors which have been shown to have an adverse influence on eBWL following RYGBP include lower educational level and patients whose jobs require them to work in shifts as opposed to a routine 9 to 5 workday.[39 40]

Gender

Those studies which have analysed the impact of gender on outcome have reported results ranging from a slightly greater degree of weight loss in male subjects to no significant difference.[24 26] Like age and race however, no meta-analyses have yet been performed on this topic.

Marital status

The final demographic factor which has been shown to influence eBWL following RYGBP is marital status. Whether this should be viewed as a modifiable factor is open to debate but the discovery that unmarried patients achieved a higher degree of eBWL after laparoscopic RYGBP when compared with their married counterparts is still worthy of consideration (table 1).[27 41]

EATING-RELATED BEHAVIOURAL FACTORS

Binge eating

In terms of the effects of preoperative behavioural factors on success rates following bariatric surgery by far the most research has been done looking at eating behaviours. The specific aspect of eating behaviour that has attracted the most attention has been that of binge eating disorder (BED) in which a person experiences episodes of eating an objectively large amount of food in association with a subjective feeling of loss of control.[42 43] A literature review in 1998 by Hsu *et al*[42] concluded that BED was associated with weight regain and suggested that further study to improve patient selection was necessary. A recent systematic review of the effects of BED on bariatric surgery as a whole by Mercado *et al*[44] found two studies reporting a positive correlation (BED being associated with greater postoperative eBWL), four studies reporting a negative correlation and 14 showing no difference. This finding would appear to be consistent with the few papers looking specifically at eBWL following RYGBP in which some have shown a negative correlation and others have shown no difference.[45–47] No meta-analyses on this topic are currently available. Interestingly, a recent study by Ashton *et al*[43] suggested that a preoperative BED intervention programme can have a beneficial effect on eBWL in those who respond compared with non-responders although this finding is at odds with those of Mercado *et al*[44] in that it assumes a negative correlation between BED and postbariatric surgery BWL.

Snacking

A less commonly studied aspect of eating behaviour is that of snacking, or grazing. Part of the reason for this may lie in the fact that there is no universally accepted definition of exactly what 'snacking' is which has implications with regard to determining the influence such behaviour has on the development, and presumably treatment, of obesity.[48–50] Two separate studies have shown that snacking behaviour *postoperatively* was associated with reduced weight loss and weight regain respectively

Table 1 Summary of the influences of patient demographic factors on eBWL following Roux-en-y gastric bypass

Group	Factor	Influence on eBWL	Based on meta-analysis
Patient demographics	Age	Variable	No
	Race	Caucasians=Hispanics, both >Afro-Caribbean subjects	No
	Socioeconomic status	No difference between public or privately funded –ve correlation with less education and shift work	No
	Gender	Slightly greater in males to no difference	No
	Marital status	Greater in single/divorced	No

eBWL, excess bodyweight loss.

but studies determining the effects of preoperative snacking behaviour on postoperative weight loss are lacking.[51 52]

OTHER BEHAVIOURAL FACTORS

Physical activity

Although several studies exist demonstrating the positive influence bariatric surgery has on postoperative physical activity levels and vice versa, few studies have attempted to clarify the relationship between preoperative physical activity levels and the degree of weight loss following surgery.[41 53] The few studies that have been published have suggested that a reduced level of physical activity preoperatively is a strong predictor of decreased eBWL following RYGBP.[39 41]

Outpatient attendance

There are very few studies looking at the influence of preoperative outpatient appointment compliance as a predictor of postoperative outcome. The only notable study on this topic was that of El Chaar *et al*[54] who compared RYGBP patients with gastric band patients and found that while gastric band patients who had missed more than a quarter of their preoperative clinic appointments had a significantly lower postoperative eBWL than those who missed fewer than 25%, the same was not true for those who had undergone the RYGBP.

Smoking

Although the precise mechanism remains unclear, the relationship between smoking cessation and weight gain is well established.[55] The health benefits of smoking cessation, however, have been shown to far outweigh the detrimental effects of that of weight gain which tends to be less than 6 kg and is rarely excessive.[56–58] Additionally, since smoking is also known to be a risk factor for postsurgical morbidity and mortality in general, and stopping smoking, even for a short period before surgery, has been shown to improve operative safety, bariatric patients who are current smokers tend to be advised to stop prior to their operation.[56 59–61] Perhaps not unreasonably therefore, most studies looking at the effects of preoperative smoking behaviour in bariatric patients have concentrated on its effects in terms of safety rather than its effects on eBWL. Those studies which have looked specifically at the effects of smoking on eBWL have found results varying from a modestly beneficial effect of smoking to a modestly detrimental effect (table 2).[33 56 62]

GENETIC INFLUENCES

Several genes have been identified as being associated with the development of obesity and its associated comorbidities; however, few studies exist which have sought to clarify their usefulness as prognostic indicators following bariatric surgery. However, despite the lack of data looking explicitly at specific genes and post-RYGBP eBWL, a small number of familial studies have been performed suggesting the existence of a genetic influence. Recently, Slotman showed that eBWL was significantly higher at 1 year post-RYGBP in genetically-related patients compared with case-matched controls.[63] Additionally, Gallagher *et al*[64] suggested that pairs of genetically-related patients are liable to achieve more similar degrees of eBWL following bariatric surgery compared with cohabiting but genetically unrelated couples. They concluded that heredity accounted for as much as 77% of the variability of postoperative eBWL.[64]

PREOPERATIVE WEIGHT STATUS

Absolute BMI

Several authors have sought to determine whether or not a patient's preoperative body mass index (BMI) and weight loss history have any bearing on their likely outcome following surgery. The majority of those studies looking solely at BMI at presentation have concluded that while a higher preoperative BMI is associated with a greater *absolute* BWL, when considered as a *proportion* the percentage eBWL among this group tends be worse.[14 24 39 65–67] Some papers however have found the opposite to be true.[68] To date no meta-analysis of the studies specific to RYGBP has been published and consequently the significance of BMI at presentation can only be considered to be based on level 3 evidence at best.[69] The discrepancy between absolute and proportional eBWL has led some authors to argue that percentage eBWL is not an appropriate measure of success in the higher initial BMI group.[70]

Preoperative BWL

Another commonly asked question seems to be: does preoperative BWL influence postoperative success? The most comprehensive attempt to answer this question was published by Livhits *et al* in 2009.[71] This systematic review found five papers showing a positive effect of preoperative BWL in terms of postoperative BWL, two papers with only an unsustained short term positive effect, five with no difference and one with a negative effect.[71] Their meta-analysis suggested that patients who had lost weight preoperatively experienced a 5% greater eBWL postoperatively at 1 year than those who did not.[71] Although this systematic review looked at bariatric surgery as a whole it is worth noting that 11 of the 13 papers (over 92% of the patients) included in the meta-analysis investigated preoperative BWL in RYGBP patients exclusively.[71] Interestingly, however, Jantz *et al*[72] suggested that the number of preoperative attempts to lose weight non-surgically was not associated with eBWL at 1 year post-RYGBP. In addition to this, Madan *et al*[73] reported that patients having to wait longer before undergoing RYGBP (and therefore with more opportunity to lose weight) do not experience any postoperative advantage in terms of eBWL. The implication from these findings would be that to delay surgery to allow patients to lose weight preoperatively offers no advantage but that encouraging them to do so anyway does. Regardless of its effect on postoperative BWL it could be argued that preoperative weight reduction should be encouraged for its other effects such as reduced intraoperative bleeding, shorter

Table 2 Summary of the influences of behavioural factors on eBWL following Roux-en-y gastric bypass

Group	Factor	Influence on eBWL	Based on meta-analysis
Behavioural	Eating-related	BED: no influence to slight −ve correlation Snacking: insufficient data	No
	Preoperative physical activity	Strong +ve correlation	No
	Preoperative clinic attendance	No effect	No
	Smoking	Variable	No

BED, binge eating disorder; eBWL, excess bodyweight loss.

Table 3 Summary of the influences of non-demographic, non-behavioural factors on eBWL following Roux-en-y gastric bypass (RYGBP)

Group	Factor	Influence on eBWL	Based on meta-analysis
Genetics	–	Insufficient data	–
Preoperative weight status	Absolute BMI	Variable	No
	Preoperative BWL	+ve correlation*	Yes
Comorbidities	DM	Slight –ve correlation	No
	Sexual abuse	–ve correlation at 1 year but no difference at 2 years	No
	Psychiatric illness	No difference	Yes
Institutional	–	No difference	No

*92% of patients in meta-analysis were RYGBP patients.
DM, diabetes mellitus; eBWL, excess bodyweight loss.

and easier surgery and fewer postoperative complications although these benefits remain unproven.[74–78]

COMORBIDITIES

Diabetes

It is well established that BWL, either surgically or non-surgically, can result in a significant reduction in the severity of diabetes mellitus (DM) and its health consequences. What is less clear is whether or not the presence of DM itself impacts on the likelihood of successfully losing weight following bariatric procedures. The largest study looking specifically at diabetics undergoing RYGBP investigated 655 patients and suggested that patients with DM, particularly those requiring insulin, experienced significantly less postoperative eBWL at 1 year than non-diabetic patients.[79] This finding has been echoed in similar studies though a few have failed to reach statistical significance.[24 39 80 81] To date no systematic review or meta-analysis looking at the predictive value of DM status as concerns post-RYGBP eBWL has been published.

History of sexual abuse

Although the exact mechanisms are not clear, there is a great deal of evidence suggesting that a history of sexual abuse in childhood is associated with an increased risk of obesity in adulthood.[82–85] It is thought that weight gain through disordered eating is used by the victims to prevent them attaining a perceived state of physical attractiveness thus defending themselves against future attacks.[84 86] Originally it was thought therefore that victims of sexual abuse, particularly those who had not undergone psychological intervention and support, would fare worse following bariatric surgery.[86 87] The majority of the literature would suggest that eBWL following RYGBP is significantly less in the abused population compared with the non-abused population at 12 months.[15 87–89] Interestingly, however, studies with longer follow-up periods have suggested that any difference seen at 12 months is eradicated by 24 months.[86 87] Although no systematic reviews or meta-analyses currently exist on this topic the general feeling is now that a history of sexual abuse should not be seen as a deterrent to bariatric intervention.[86 87]

Psychiatric comorbidities

Evaluating the impact of psychological or psychiatric comorbidity on RYGBP outcomes presents its own challenges owing to the range of conditions that can be considered, variations in diagnostic criteria, the variety of different tools that are available to assess the same or similar conditions and the fact that those affected by psychiatric illnesses are not infrequently also affected by other comorbidities which may introduce a degree of bias. Nevertheless, there is a wealth of literature looking at this topic, primarily concerned with depression and personality traits. In 2008, Ashton *et al*[90] reviewed this literature and argued that there was no good evidence to support the statement that preoperative psychological testing could predict postoperative RYGBP outcomes and therefore that the common practise of excluding patients based on the results of such testing was unjustifiable. This is in line with the conclusions of van Hout *et al* who, in a literature review 3 years earlier, stated that while outcomes tended to be better in certain patient groups than others the literature for potential predictors of success was far from conclusive.[16 90–95]

INSTITUTIONAL FACTORS

Two reviews have been published looking at the results on the Nationwide Inpatient Sample database of patients undergoing all form of bariatric intervention.[96 97] These have suggested that whether or not an institution has the status of bariatric centre of excellence has no effect on early outcomes; however, they were not designed to look at long term outcomes like eBWL.[96 97] To date, the only study to do this was published by Kothari *et al*[98] who, in a review of their community-based training hospital's data, concluded that their results compared favourably with the published literature in terms of major complications as well as eBWL and that teaching hospital status did not guarantee better long term outcomes. Clearly since this is an isolated study more evidence is required before this conclusion can be confirmed (table 3).

SUMMARY

Although many factors have been implicated as being potentially predictive of the degree of eBWL that can be expected following RYGBP, few are strongly and consistently supported in the literature. Furthermore, only a few of these factors are remediable. The importance of others, such as race, age and gender, lies in their usefulness for managing patients' expectations. Simply put, the existing data do not support the refusal of RYGBP to morbidly obese patients on the basis of demographic factors or psychiatric illness and, although the more motivated a patient is the better they are likely to do, the vast majority of patients can expect to experience some benefit.

Main messages

- Married and/or of Afro-Caribbean patients tend to lose less weight following Roux-en-y gastric bypass (RYGBP).
- The more physically active a patient is and the more weight a patient loses before surgery the more weight they can expect to lose after it.
- Psychiatric comorbidity and a history of sexual abuse are not associated with less weight loss following RYGBP.

Current research questions

- Can weight loss following bypass surgery be predicted?
- Which factors affect weight loss following bypass surgery?
- Can patient selection for weight loss surgery be optimised?

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MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. Bariatric surgery poses an extra financial burden on the NHS.
2. Losing weight before surgery has no effect on weight loss postsurgery.
3. Afro-Caribbean subjects are prone to losing less weight after bypass surgery than Caucasians or Hispanics.
4. Those patients who pay for their surgery themselves tend to lose more weight.
5. Psychological assessments provide a useful measure of the likelihood of successful weight loss after bypass surgery.

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ANSWERS

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Preoperatively determinable factors predictive of diabetes mellitus remission following Roux-en-Y gastric bypass: a review of the literature

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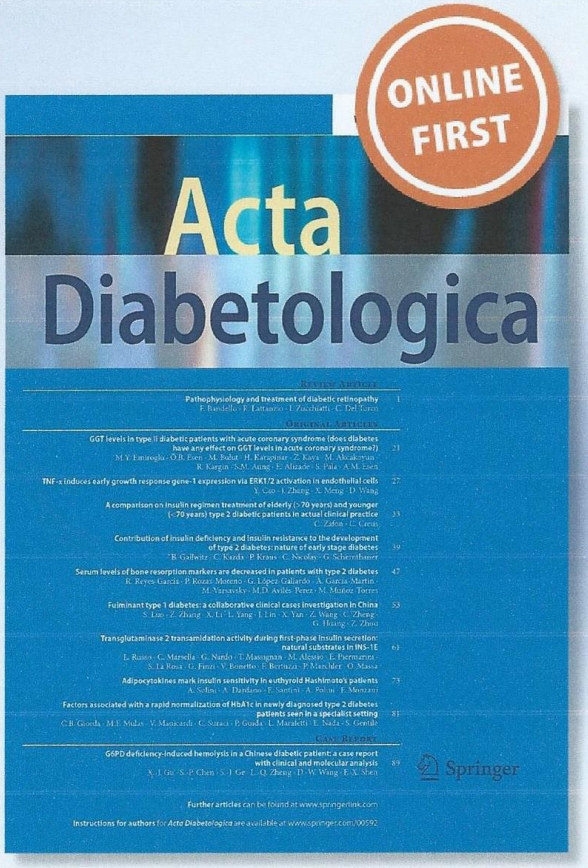

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REVIEW ARTICLE

Preoperatively determinable factors predictive of diabetes mellitus remission following Roux-en-Y gastric bypass: a review of the literature

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Abstract It is well established that weight loss in general and bariatric surgery in particular can improve glycaemic control in diabetics. Current NICE guidelines recommend that those patients with type 2 diabetes mellitus and a BMI of 35 kg/m^2 or more should be considered for bariatric surgery in order to optimise their glycaemic control and minimise their risk of long-term complications. The commonest bariatric procedure in the UK is the Roux-en-Y gastric bypass that has been shown to result in long-standing type 2 diabetes resolution in 83 % of patients. Since such surgery carries a small but significant risk of mortality, as well as posing considerable lifestyle implications for the patient, numerous studies have been performed with a view to identifying which patients and which procedures are most likely to result in these desired benefits. This paper summarises the existing literature on this topic.

Keywords Obesity · Diabetes · Bypass

Introduction

One of the main benefits of bariatric surgery is that it has been shown to reduce the severity of type 2 diabetes mellitus (DM), in some cases inducing remission lasting several years [1–3]. Indeed, the non-medical media has often touted bariatric surgery as a "cure" for diabetes although specialist medical opinion has tended to shy away from using this term [4]. The mechanisms by which such procedures result in prolonged improvement in glycaemic control have been the subject of a great deal of study with weight loss, reduced oral intake, altered hormonal secretion and changes to the gastrointestinal tract microflora all having been proposed as playing a part in this phenomenon [5–11]. Given the serious nature of the complications of DM on the cardiovascular and renal systems, the level of interest in the effects of bariatric surgery on such pathologies is perhaps unsurprising [3, 12–15].

A consensus statement released in 2009 by a panel of expert endocrinologists defined remission of type 1 and type 2 DM as glycaemia below the diabetic range in the absence of pharmacological or surgical therapy [4]. Partial remission was defined as sub-diabetic hyperglycaemia (HbA1c <6.5 %, fasting glucose 5.6–6.9 mmol/l (or ≥99 and ≤126 mg/dl)) of at least 1 year's duration, and complete remission was defined as a full return to normal measures of glucose metabolism (normal HbA1c, fasting glucose <5.6 mmol/l) for the same duration [4]. Prolonged remission was considered to be complete remission lasting 5 or more years [4].

Bariatric surgery in diabetics

Presently, 366 million people worldwide are thought to be affected by DM [16]. A large proportion of these people are also obese and therefore eligible for potential remission inducing bariatric surgery. A meta-analysis by Buchwald et al. [1] looking at bariatric surgery as a whole showed complete remission of type 2 DM at 2-year follow-up in 78.1 % of patients and improvement in a further 8.5 %

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with excess bodyweight loss (eBWL) and DM remission rates being greatest in the duodenal switch patients, then in the Roux-en-Y gastric bypass (RYGBP) patients and worst in those undergoing gastric banding. Similar results were reported in a systematic review by Meijer et al. [3] which showed DM remission in 83 % of RYGBP patients and 62 % of gastric band patients at 2–14-year follow-up. Although most of the literature on this topic has focused on results over the first few postoperative years, those few studies with longer follow-up periods have shown that the phenomenon of DM remission persists—for example, Pories et al. [17] reported a case series in which 82.9 % of previously diabetic patients who had undergone RYGBP had normal glucose homoeostasis parameters at 10–14 years [2, 17–18]. It should be noted, however, that all of these papers refer to the data either published or collected prior to the publication of the revised criteria for DM remission described above. The reason why this may be significant is that Pournaras et al. [19] presented data in 2011 in which patients showed only a 34 % complete DM remission rate at 1 year according to the new criteria (41 % for RYGBP, 26 % for sleeve gastrectomy and 7 % for gastric banding) suggesting that a revision of the expectations post-bariatric surgery may be necessary for patients and clinicians alike.

Given the impressive results in the obese population with DM, it is perhaps unsurprising that recently attention has been paid to determining whether or not other groups of diabetics would experience similar benefits. To date, the only study to investigate the effects of RYGBP on obese patients with type 1 DM reported that 4 of the 5 patients with the condition (out of 2,170 in the series) experienced a reduction in insulin requirements at 3–76 months follow-up (mean 29 months) [20]. Their mean eBWL was 58.9 % (range 47.1–82 %) [20]. Clearly, however, the numbers involved in this study make it difficult to draw any firm conclusions. In stark contrast, however, there is increasing evidence to suggest that patients with type 2 DM with body mass indexes (BMIs) below the current cut-off point for bariatric surgery as defined by NICE guidelines may benefit more than initially thought [21, 22]. A review of the literature published by Reis et al. [23] found that improvements in glycaemic control in the BMI <35 group were seen with a range of different bariatric techniques.

Predictors of remission

Short term

In comparison with studies looking primarily at eBWL, there is a relative paucity of studies attempting to identify predictive factors for the remission of DM. The best attempt to establish a predictive model for this issue was published by Hayes et al. in 2011 [24]. Hayes et al. [24] used 13 preoperative parameters and a variety of statistical and data mining techniques to create 6 different mathematical models [24]. These models were able to correctly identify which patients would experience remission of their DM at 12 months follow-up in 82.7–87.4 % of cases. The most accurate model was a decision tree based on DM status (unrecognised, diet controlled, tablet controlled or insulin controlled), fasting glucose levels, HbA1c, and whether or not the patient had concomitant hypertension [24]. The two strongest predictors of DM resolution were low HbA1c and no requirement for insulin therapy which were used in all 6 of the models and were the only factors used for 3 of them [24]. These two factors alone successfully predicted DM remission in 86.6 % of cases in 2 of these 3 models [24]. Interestingly, Hayes et al. [24] also found that a lower preoperative BMI was a negative predictor of DM resolution which clearly could have important implications for clinicians with regard to patient selection and the indications for surgery.

Another study addressing the issue of prediction of DM remission would be Hamza et al. [25] who reported that the percentage of postoperative eBWL was the only predictor of DM remission influenced by the choice of procedure and that the only other independent predictor was younger age. The finding that greater eBWL results in improved DM remission rates echoes that of a previous study by Kadera et al. [26] although clearly this finding is of little relevance to those seeking to predict DM remission in preoperative patients. Similar findings regarding patient age were presented by Lee et al. [27] who proposed that not only did younger age confer an increased chance of DM remission but also that having a shorter duration of DM was an independent predictor. This finding too has been supported in subsequent studies [26, 28].

Other factors which have been found to be significantly associated with the chances of DM remission following RYGBP include the nature and level of preoperative DM control. Several studies, including Maciejewski et al. [29], have reported that those RYGBP patients most likely to have discontinued their DM medication at 1 year postoperatively were those who were treated preoperatively with oral hypoglycaemic agents alone, followed by those on insulin alone and lastly those on both forms of treatment [30]. Kadera et al. [26] went one step further and suggested that not only did insulin requirement *per se* significantly influence the chances of remission versus mere improvement of DM control but also that insulin dose significantly differed between the 2 groups. It is perhaps noteworthy that although all 6 of the models proposed by Hayes et al. [24] used preoperative HbA1c in their analyses, other studies have found no significant association between this factor and DM remission [26]. Similarly, whilst Hall et al. [28]

reported a significant difference in remission rates between those with a preoperative HbA1c >10 % compared to those for whom it was between 6.5 and 7.9 %, the lowest rate of DM remission was seen in those patients whose levels fell between these two groups. It has been proposed that a more predictive accurate measurement would be the homeostatic model of assessment estimated glucose disposition index (HOMA-DI), which is the product of insulin sensitivity and beta-cell sensitivity; however, presently, this measurement is not in common use, and there is little evidence in the literature to support this suggestion [31, 32].

Long term

As discussed in the opening paragraph, the term "remission of diabetes" is preferred to the use of the word "cure" as it implies the potential for the re-emergence of abnormal glucose homoeostasis in the future. To date, there exist only a handful of papers looking at predictive factors for the long-term durability of DM remission. Chikunguwo et al. [33] investigated 157 patients whose type 2 DM had gone into remission at 1-year post-RYGBP and found that prolonged remission existed in 57 % of them. Echoing the conclusions of studies looking at short-term remission, they found that durable remission was most likely in those patients whose DM was initially controlled by diet alone, followed by those on oral hypoglycaemic agents alone and finally by those requiring insulin [33]. Prolonged DM remission was also significantly more likely in men than in women [33]. Low eBWL, weight regain and older age were weak predictors of remission [33]. In a similar but smaller study using a shorter follow-up period, DiGiorgi et al. [34] found comparable results to Chikunguwo et al. [33] in terms of reduced durability of remission in those patients who experienced less postoperative eBWL or weight regain (Table 1).

One potential confounding factor common to each of the above studies is that it is assumed that the patients in the study populations had type 2 DM rather than latent autoimmune diabetes of the adult (LADA) [35]. LADA is a form of type 1 DM in which there is gradual autoimmune destruction of the pancreatic beta-cells over a period of up to 12 years rather than the peripheral insulin resistance characteristic of type 2 DM [35, 36]. Because of the slow progression of the disease, many patients are erroneously diagnosed with type 2 DM, whereas in actuality in 10 % of the phenotypically type 2 DM, population over age the age of 35 and 25 % of those below it LADA is the true diagnosis [35, 36].

Table 1 Showing preoperative predictors of DM remission following RYGBP in the short and long terms

	Positively associated with DM remission	Negatively associated with DM remission
Short term	Mode of DM control (diet > tablet > insulin (low dose > high dose))	Lower preoperative BMI
	Good glycaemic control (fasting glucose/HbA1c)	Concomitant hypertension
	Younger age at surgery	
	Shorter duration since onset of DM	
Long term	Mode of DM control (diet > tablet > insulin)	
	Gender (male > female)	

Summary

Whilst it seems to be universally accepted that all forms of surgical and non-surgical BWL improve type 2 DM, albeit to varying degrees, the exact mechanisms by which they do this remain a source of controversy. There is strong evidence to support the idea that the less severe and short-lived a patient's DM is then the greater their chances of achieving a sustained, complete remission following surgery. Whether or not there are any other predictive factors that could be used to identify those individuals most likely to benefit from surgically induced BWL is presently unknown.

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Appendix 15: Raw Data

Hospital	Clinic	Recruited	Age	Gender	Height	BW	BMI	Preop HbA1c	PreopSystolic	PreopDiastolic
YDH	07.05.10	07.05.10	27	female	1.61	133.6	51.5	39.9	110	71
YDH	22.10.10	22.10.10	56	male	1.8	140	43.2	59.6	175	74
CHH	12.10.10	12.10.10	43	female	1.55	135.9	56.6		131	80
YDH	07.05.10	07.05.10	62	male	1.73	127.5	42.6	51.9	135	72
CHH	12.10.10	11.05.10	45	female	1.64	105.6	39.3		155	97
CHH	11.05.10	11.05.10	53	female	1.56	99.6	40.9		170	96
CHH	11.05.10	11.05.10	50	female	1.48	92.9	42.4		120	74
CHH	14.09.10	14.09.10	69	female	1.62	120	45.7		122	70
CHH	11.05.10	11.05.10	30	female	1.59	108.2	42.8			
YDH	18.06.10	16.09.10	42	female	1.71	136.9	46.8	63.9	164	96
CHH	11.05.10	11.05.10	63	male	1.79	152.2	47.5	56.3	175	80
CHH	28.09.10	28.09.10	30	female	1.69	109.9	38.5		128	95
CHH	25.05.10	25.05.10	62	male	1.77	150	47.9		132	87
CHH	25.05.10	25.05.10	52	male	1.87	162.1	46.4		132	83
CHH	25.05.10	25.05.10	42	female	1.65	145	53.3	62.8	156	88
CHH	25.05.10	25.05.10	37	male	1.86	145	41.9	58.5		
YDH	28.05.10	28.05.10	65	female	1.54	111.6	47.1	48.6	131	69
CHH	12.10.10	12.10.10	28	female	1.63	146	55		132	88
YDH	28.05.10	28.05.10	25	female	1.8	160	49.4	37.7	136	80
YDH	28.05.10	28.05.10	30	female	1.76	132.8	42.9			
CHH	30.06.10	30.06.10	18	female	1.61	127.7	49.3		121	81
CHH	30.06.10	30.06.10	22	male	1.69	166.8	58.4			
YDH	22.10.10	22.10.10	56	female	1.54	91.5	38.6	41	113	85
CHH	19.07.10	19.07.10	38	male	1.87	160.8	46			
YDH	04.06.10	16.07.10	60	male	1.81	154.9	47.3	39.9	155	83
YDH	16.07.10	16.07.10	64	female	1.65	121.5	44.6			
YDH	16.07.10	16.07.10	47	female	1.59	114	45.1	36.6	123	72
YDH	16.07.10	16.07.10	42	female	1.6	128.3	50.1	37.7	124	62
YDH	16.07.10	16.07.10	39	female	1.52	93.1	40.3			
CHH	19.07.10	19.07.10	55	female	1.64	115.2	42.8	36.6	140	85
CHH	19.07.10	19.07.10	42	female	1.64	126.4	47	65	161	89
CHH	19.07.10	19.07.10	47	male	1.8	166.4	51.4		148	98
YDH	22.10.10	22.10.10	24	female	1.77	151	48.2			
YDH	04.08.10	25.10.10	34	male	1.91	161.8	44.4	37.7	137	87
YDH	04.08.10	25.10.10	42	female	1.57	152	61.7			
YDH	06.08.10	06.08.10	47	female	1.63	167.5	63	59.6	179	88
YDH	06.08.10	06.08.10	34	female	1.6	150	58.6	42.1	151	81
YDH	06.08.10	06.08.10	43	female	1.63	149	56.1	54.1	130	83
YDH	06.08.10	06.08.10	42	female	1.66	107.9	39.2	54.1	125	76
YDH	20.08.10	20.08.10	42	female	1.7	158.7	54.9	38.8	165	76
YDH	28.10.10	28.10.10	41	female	1.71	170	58.1	44.3	132	59
YDH	20.08.10	20.08.10	25	female	1.64	167.5	62.3	38.8	161	89
YDH	27.08.10	27.08.10	45	female	1.69	151.8	53.1	43.2	141	88
YDH	27.08.10	27.08.10	40	female	1.6	108	42.2	36.6	124	66
YDH	27.08.10	27.08.10	46	female	1.56	129.5	53.2	54.1	135	79
YDH	27.08.10	27.08.10	41	female	1.71	117.7	40.3			
YDH	04.06.10	09.09.10	39	female	1.52	141.7	61.3	41	142	82
YDH	11.06.10	10.09.10	66	female	1.65	138	50.7	46.4	112	67
YDH	04.08.10	12.11.10	43	female	1.69	146.3	51.2	54.1	133	79
YDH	10.12.10	10.12.10	56	male	1.61	131	50.5	57.4	122	65
YDH	10.09.10	10.09.10	58	female	1.6	136	53.1	30.1	195	81
YDH	10.09.10	10.09.10	55	female	1.66	124	45			
YDH	30.07.10	28.10.10	59	female	1.6	126.1	49.3	46.4	179	71
YDH	29.10.10	29.10.10	42	female	1.63	117.4	44.2	36.6	179	95
YDH	29.10.10	29.10.10	49	female	1.6	129.6	50.6	45.4	117	80
YDH	29.10.10	29.10.10	28	female	1.73	167.8	56.1	38.8	158	73
YDH	29.10.10	29.10.10	43	female	1.59	114.9	45.4			
YDH	12.11.10	12.11.10	34	female	1.63	132.5	49.9	41	225	99
YDH	12.11.10	12.11.10	29	female	1.58	138.3	55.4	36.6	143	71
YDH	20.08.10	20.08.10	24	female	1.7	157.4	54.5	44.3	110	75
YDH	12.11.10	12.11.10	35	female	1.65	122.4	45	39.9	121	58
YDH	25.11.10	25.11.10	60	female	1.66	122.4	44.4			
YDH	13.08.10	16.11.10	37	male	1.65	117.1	43	34.4	138	82
YDH	13.08.10	15.11.10	46	female	1.56	106.2	43.6	48.6	126	90

13.08.10	15.11.10	39	female	1.67	121	43.4	46.4	200	91
19.11.10	19.11.10	38	female	1.64	116.9	43.5	33.3	133	62
19.11.10	19.11.10	58	female	1.66	152.5	55.3	47.5	205	100
18.06.10	19.11.10	52	female	1.59	101.5	40.1	61.7	125	76
12.03.10	19.11.10	37	female	1.65	133	48.9	38.8	142	73
23.11.10	23.11.10	56	female	1.67	117.7	42.2		134	85
23.11.10	23.11.10	42	female	1.65	162.4	59.7		117	76
26.11.10	26.11.10	40	female	1.67	117.4	42.1	34.4	123	73
23.11.10	23.11.10	47	female	1.58	131.8	52.8		134	76
26.11.10	26.11.10	25	female	1.54	107.6	45.4			
26.11.10	26.11.10	47	female	1.66	155.5	56.4	32.2	152	68
26.11.10	26.11.10	36	female	1.64	135.5	50.4	24.6	131	77
03.09.10	30.11.10	38	female	1.66	129.7	47.1	46.4	117	72
03.09.10	09.12.10	42	female	1.5	105	46.7	41	137	74
13.08.10	13.12.10	56	male	1.8	124	38.3	35.5	153	92
17.12.10	17.12.10	47	female	1.75	106.7	34.8			
17.12.10	17.12.10	17	female	1.72	145	49	35.5	172	79
17.12.10	17.12.10	42	female	1.59	128.8	50.9	31.1	150	95
17.12.10	17.12.10	46	female	1.6	111.9	43.7			
17.09.10	17.12.10	42	female	1.62	149	56.8	113.1	158	84
17.09.10	17.12.10	39	female	1.65	149	54.7	45.4	98	78
20.12.10	20.12.10	49	male	1.77	149.8	47.8	67.2	150	101
10.06.10	30.12.10	55	female	1.59	162	64.1			
31.12.10	31.12.10	49	female	1.6	122.6	47.9	34.4	135	73
31.12.10	31.12.10	35	female	1.62	143.9	54.8	29	143	77
31.12.10	31.12.10	53	female	1.57	105.3	42.7	24.6	144	88
31.12.10	31.12.10	50	male	1.75	153.5	50.1	29	127	71
07.01.11	07.01.11	44	male	1.7	133	46	78.1	154	83
07.01.11	07.01.11	50	male	1.8	170	52.5	54.1	173	106
11.01.11	11.01.11	27	male	1.79	168	52.4	44.3	141	89
08.10.10	11.01.11	51	female	1.61	139	53.6			
14.01.11	14.01.11	42	female	1.64	147	54.7	47.5	142	63
14.01.11	14.01.11	29	female	1.65	141	51.8	37.7	134	73
14.01.11	14.01.11	60	female	1.63	134	50.4	62.8	151	77
04.08.10	14.01.11	63	female	1.65	128	47	50.8	150	75
18.01.11	18.01.11	34	female	1.77	174.2	55.9	29	183	100
18.01.11	18.01.11	27	female	1.65	135.6	49.8		124	74
18.01.11	18.01.11	62	male	1.68	136.8	48.5			
18.01.11	18.01.11	41	female	1.64	127.4	47.4		132	86
18.01.11	18.01.11	63	female	1.59	125.7	49.7		163	91
25.02.11	25.02.11	24	female	1.56	132.8	54.6	43.2	177	84
25.02.11	25.02.11	43	female	1.67	144	51.6	31.1	128	84
25.02.11	25.02.11	42	male	1.76	134	43.3			
04.03.11	04.03.11	54	female	1.68	122.7	43.5			
04.03.11	04.03.11	43	male	1.73	159	53.1	24.6		
04.03.11	04.03.11	46	male	1.72	141	47.7	106.6	121	66
04.03.11	04.03.11	36	male	1.79	164.2	51.2	25.7	135	62
18.06.10	10.03.11	42	male	1.85	150	43.8	33.3	175	102
11.03.11	11.03.11	48	female	1.62	148	56.4	22.4	158	90
15.03.11	15.03.11	36	male	1.89	198	55.4	27.9	135	80
15.03.11	15.03.11	55	male	1.67	117.2	42	25.7	107	73
15.03.11	15.03.11	63	male	1.71	222.7	76.2		149	87
18.03.11	18.03.11	44	female	1.63	137	51.6	55.2	169	86
18.03.11	18.03.11	47	male	1.74	159.3	52.6	73.8	167	95
25.03.11	25.03.11	67	male	1.76	153	49.4			
25.03.11	25.03.11	46	female	1.75	156.7	51.2	39.9	151	70
16.04.10	25.03.11	42	female	1.57	142.2	57.7	33.3	117	67
08.10.10	14.04.11	34	male	1.77	179.8	57.4			
28.01.11	03.05.11	52	female	1.6	125.5	49			
21.09.10	05.05.11	38	female	1.62	123	46.9	33.3	153	75
18.02.11	16.05.11	60	female	1.63	98.8	37.2			
18.02.11	16.05.11	51	female	1.53	88	37.6	47.5	108	74
30.07.10	23.05.11	48	male	1.7	157.7	54.6	45.4	135	86
11.02.11	27.05.11	62	female	1.6	123	48			
11.02.11	27.05.11	27	female	1.71	199	68.1	46.4	226	134

Genetic	Ethnicity	Reason	2nd	TFEQ	Cognitive	Uncontrol	Emotional
49	mixed rac	life expec	quality of	39	11	19	9
7	caucasian	life expec	appearanc	39	11	22	6
32	caucasian	quality of	comorbidi	32	13	16	3
27	caucasian	comorbidi	other	42	11	22	9
5	caucasian	comorbidi	quality of	54	14	31	9
17	caucasian	quality of	comorbidi	44	15	18	11
12	caucasian	life expec	quality of	25	8	14	3
79	caucasian	appearanc	other	36	17	14	5
32	caucasian	comorbidi	appearanc	41	15	20	6
12	caucasian	life expec	comorbidi	45	14	22	9
37	caucasian	comorbidi	quality of	35	14	16	5
15	caucasian	comorbidi	quality of	40	16	18	6
12	caucasian	quality of	other	33	19	11	3
58	caucasian	quality of	life expec	51	11	31	9
66	caucasian	life expec	other	38	13	17	8
45	caucasian	life expec	other	55	14	30	11
29	caucasian	comorbidi	quality of	54	12	31	11
60	caucasian	quality of	life expec	50	18	23	9
15	caucasian	comorbidi	quality of	53	21	28	4
45	caucasian	appearanc	comorbidi	51	16	26	9
52	caucasian	quality of	other	47	9	28	10
44	caucasian	quality of	comorbidi	29	10	16	3
26	caucasian	quality of	life expec	38	17	15	6
9	caucasian	quality of	other	37	13	16	8
73	caucasian	life expec	quality of	46	17	21	8
21	caucasian	comorbidi	quality of	31	15	11	5
52	caucasian	comorbidi	appearanc	34	15	14	5
22	caucasian	life expec	quality of	46	15	22	9
9	mixed rac	life expec	quality of	50	15	26	9
20	caucasian	comorbidi	other	27	9	15	3
43	caucasian	comorbidi	quality of	37	12	17	8
66	caucasian	comorbidi	quality of	49	20	20	9
45	caucasian	comorbidi	quality of	42	15	19	8
27	caucasian	appearanc	other	44	16	25	3
5	caucasian	quality of	comorbidi	33	21	9	3
33	caucasian	comorbidi	quality of	45	16	20	9
25	caucasian	comorbidi	other	42	12	18	12
58	caucasian	comorbidi	quality of	38	8	23	7
64	caucasian	comorbidi	other	42	14	22	6
17	caucasian	comorbidi	quality of	34	14	14	6
30	caucasian	comorbidi	life expec	39	12	18	9
65	caucasian	comorbidi	other	56	14	30	12
32	caucasian	comorbidi	life expec	45	14	22	9
52	caucasian	comorbidi	quality of	46	16	23	7
79	caucasian	comorbidi	quality of	44	12	23	9
46	caucasian	life expec	quality of	31	12	13	6
44	caucasian	life expec	quality of	49	15	23	11
13	caucasian	comorbidi	appearanc	40	6	22	12
45	caucasian	quality of	comorbidi	39	17	14	8
31	caucasian	comorbidi	other	31	15	12	4
19	caucasian	quality of	appearanc	46	17	23	6
10	caucasian	comorbidi	quality of	40	16	18	6
79	caucasian	comorbidi	other	33	16	11	6
7	caucasian	quality of	appearanc	42	17	22	3
0	caucasian	quality of	life expec	44	16	21	7
30	caucasian	life expec	other	49	10	31	8
90	caucasian	comorbidi	life expec	41	16	19	6
55	caucasian	comorbidi	appearanc	53	8	33	12
61	caucasian	quality of	appearanc	36	6	22	8
47	caucasian	quality of	comorbidi	29	17	9	3
48	caucasian	quality of	comorbidi	49	13	26	10
56	caucasian	comorbidi	other	60	15	36	9
26	caucasian	comorbidi	appearanc	28	13	12	3
17	caucasian	comorbidi	quality of	42	16	20	6

6	caucasian	quality of	life expec	53	12	29	12
29	caucasian	life expec	comorbidi	57	13	32	12
0	caucasian	quality of	other	50	18	23	9
0	caucasian	comorbidi	quality of	42	18	16	8
29	caucasian	appearanc	quality of	51	15	28	8
14	caucasian	comorbidi	other	32	14	12	6
19	caucasian	comorbidi	quality of	44	12	23	9
7	caucasian	comorbidi	other	41	12	23	6
29	caucasian	comorbidi	other	47	15	22	10
59	asian	quality of	comorbidi	46	17	17	12
15	caucasian	comorbidi	quality of	39	16	15	8
43	caucasian	quality of	appearanc	38	15	16	7
18	caucasian	quality of	appearanc	46	15	22	9
30	caucasian	quality of	comorbidi	42	11	23	8
8	caucasian	comorbidi	life expec	44	14	25	5
42	caucasian	quality of	comorbidi	51	13	32	6
68	caucasian	quality of	comorbidi	46	10	24	12
42	caucasian	comorbidi	other	30	10	17	3
5	caucasian	comorbidi	quality of	36	18	13	5
79	caucasian	quality of	comorbidi	45	14	21	10
59	caucasian	quality of	comorbidi	49	13	25	11
27	caucasian	comorbidi	quality of	46	9	30	7
20	caucasian	quality of	other	31	7	21	3
29	caucasian	comorbidi	life expec	33	20	10	3
66	caucasian	comorbidi	quality of	38	17	13	8
45	caucasian	quality of	comorbidi	36	15	15	6
0	caucasian	comorbidi	quality of	33	20	10	3
66	caucasian	comorbidi	quality of	34	20	10	4
30	caucasian	comorbidi	other	45	18	19	8
48	asian	life expec	quality of	43	19	18	6
10	caucasian	appearanc	comorbidi	41	19	16	6
22	caucasian	life expec	comorbidi	46	8	29	9
34	caucasian	appearanc	quality of	49	12	28	9
50	caucasian	life expec	quality of	48	15	21	12
7	caucasian	comorbidi	quality of	51	19	23	9
75	caucasian	quality of	comorbidi	39	10	20	9
82	caucasian	quality of	comorbidi	55	11	32	12
22	caucasian	comorbidi	quality of	50	16	26	8
38	caucasian	quality of	comorbidi	49	10	27	12
0	caucasian	comorbidi	other	45	20	17	8
46	caucasian	comorbidi	other	41	14	19	8
57	caucasian	life expec	other	38	8	21	9
15	caucasian	other	appearanc	50	9	31	10
54	caucasian	life expec	comorbidi	41	12	21	8
14	caucasian	comorbidi	quality of	36	17	16	3
86	caucasian	life expec	quality of	51	15	27	9
64	caucasian	quality of	life expec	39	15	19	5
49	caucasian	comorbidi	life expec	45	13	23	9
86	caucasian	comorbidi	quality of	52	15	26	11
70	caucasian	appearanc	comorbidi	41	14	22	5
33	caucasian	comorbidi	other	51	17	25	9
4	caucasian	quality of	appearanc	42	18	15	9
12	caucasian	quality of	comorbidi	51	10	29	12
20	caucasian	comorbidi	life expec	25	12	10	3
12	caucasian	comorbidi	other	42	16	17	9
49	caucasian	comorbidi	quality of	41	6	23	12
85	caucasian	comorbidi	life expec	45	13	22	10
41	caucasian	quality of	life expec	39	12	24	3
36	caucasian	quality of	life expec	43	13	21	9
28	caucasian	quality of	life expec	33	13	11	9
19	caucasian	life expec	comorbidi	36	21	10	5
35	caucasian	comorbidi	quality of	41	18	15	8
29	caucasian	comorbidi	quality of	45	18	20	7
30	caucasian	comorbidi	life expec	47	14	22	11
83	caucasian	quality of	life expec	41	18	16	7

BPAQ	Work	Sport	Leisure	Physical	Vitality	Relations	Psych	OSQOL
40	3	1.5	2.5	330.7	460.7	23.9	-42.2	773.2
23	0	2.5	3.25	584.8	263.1	179.3	147.5	1174.6
11	0	1	1.75	740.3	460.7	83.6	147.5	1432.2
29	1.88	1.75	1.75	440.6	263.1	179.3	147.5	1030.4
46	3	1.75	3.75	249.1	147.2	83.6	42.2	522
39	2.25	1.5	3.75	-166.8	147.2	83.6	147.5	211.5
20	0	2	3	67	57.1	-107.6	-189.7	-173.1
18	0	1.25	3.25	366.7	75.2	83.6	42.2	567.6
16	0	1.75	2.25	298	344.8	-23.9	42.2	661.1
41	3.13	1.5	2.5	616	460.7	179.3	316.1	1572.1
43	3.25	1.75	2.5	559.5	198.7	83.6	-42.2	799.7
60	3.75	4.5	3	-214.1	-75.2	-23.9	-42.2	-355.3
43	3.25	2.5	1.75	292.5	147.2	23.9	42.2	505.8
39	2.75	1.75	2.5	18.6	-75.2	-23.9	-42.2	-122.6
29	2.25	1.25	1.5	803.2	366.1	83.6	147.5	1400.4
20	0	3	2	-144.4	198.7	23.9	42.2	120.4
27	2.25	1	1.25	612.1	460.7	179.3	147.5	1399.5
40	3.13	2	1.75	572.7	344.8	83.6	316.1	1317.3
36	2.38	1.75	2.5	515.1	460.7	83.6	147.5	1207
20	0	2.25	2.75	263	263.1	23.9	42.2	592.2
49	3.5	2.75	2.5	176.8	263.1	83.6	316.1	839.6
26	1.75	1.75	1.25	443.2	366.1	-107.6	-42.2	659.5
49	3	2.25	4	-166.4	-165.3	-23.9	-42.2	-397.8
13	0	1.5	1.75	701	563.7	23.9	147.5	1436.1
39	2.88	1.5	2.5	123.4	-75.2	-23.9	-189.7	-165.3
12	0	1.25	1.75	740.3	460.7	179.3	316.1	1696.4
52	3.63	3.25	2.5	-250.8	-66.5	83.6	42.2	-191.4
45	3.63	1.75	2.25	-17.6	57.1	23.9	147.5	210.9
42	3.13	1.75	2.5	424.2	460.7	83.6	147.5	1116.1
41	2.63	2.75	2.25	-220.5	263.1	-107.6	-189.7	-254.6
16	0	1.25	2.75	165.1	396.3	23.9	147.5	732.9
44	3.63	1.75	2	266.2	198.7	83.6	316.1	864.6
44	3.13	2	2.75	116.3	147.2	-23.9	147.5	387.1
31	1.75	2.25	2	101	139.5	-107.6	42.2	175.1
44	2.5	2.75	3.25	358.7	147.2	23.9	-189.7	340.1
15	0	1.5	2.25	559.8	263.1	23.9	147.5	994.3
37	3.38	1	1.5	409.3	563.7	-23.9	147.5	1096.6
44	3.75	1	2.5	401.6	344.8	83.6	316.1	1146.2
13	0	1.25	2	479.6	460.7	179.3	316.1	1435.7
17	0	2.75	1.5	576.7	460.7	23.9	147.5	1208.8
37	3	1.5	1.75	518.6	198.7	23.9	42.2	783.3
38	2.25	2.25	2.75	346	460.7	23.9	147.5	978.2
41	3.75	1	1.75	424.2	198.7	83.6	42.2	748.7
43	3.88	1	2	145.8	396.3	179.3	147.5	868.9
9	0	1.25	1.5	672.1	263.1	23.9	42.2	1001.2
36	3	1	2	589.3	198.7	83.6	147.5	1019.1
30	2.13	1.25	2	173.1	139.5	83.6	147.5	543.8
23	1.88	0.75	1.25	684.7	563.7	179.3	42.2	1469.8
20	0	1.5	3.5	-106.2	-66.5	23.9	42.2	-106.6
15	0	0.75	3	514.2	263.1	83.6	147.5	1008.4
47	3.75	1.5	2.75	-0.5	-165.3	179.3	-42.2	-28.6
31	2.5	1.25	1.5	200.8	263.1	23.9	-189.7	298.1
27	2.38	1	1	694.6	563.7	83.6	42.2	1384.1
29	2.38	1	1.5	632.6	563.7	83.6	42.2	1322.1
30	2.13	1	2.25	202.9	263.1	83.6	147.5	697.1
41	3.63	1.75	1.25	-238.2	198.7	-23.9	-189.7	-253.1
32	2.38	1.25	2	308.3	147.2	83.6	316.1	855.2
35	2.75	1.25	2	216.4	563.7	83.6	147.5	1011.3
32	2.88	0.75	1.5	377.5	563.7	83.6	147.5	1172.4
39	3.13	1	2.5	-154.6	-66.5	83.6	147.5	10.1
58	4.38	3	2.75	189.8	147.2	179.3	-42.2	474.1
52	3.25	3.25	3.25	397.8	263.1	83.6	42.2	786.7
37	2.63	1.75	2.25	-17.8	344.8	83.6	147.5	558.2
34	2.38	1.25	2.5	571.6	263.1	83.6	42.2	960.4

46	3.38	2.5	2.25	304.6	563.7	83.6	316.1	1268.1
52	4.5	1.75	2.25	527.3	460.7	83.6	42.2	1113.8
23	1.75	0.75	1.5	803.2	563.7	179.3	316.1	1862.3
47	3.38	1.5	3.5	-24.4	-75.2	-23.9	-42.2	-165.6
30	2	1	2.5	545.8	460.7	83.6	147.5	1237.7
48	4	1	3	350.9	254.7	23.9	42.2	671.6
24	1.63	1.75	1	684.7	563.7	83.6	316.1	1648.2
39	2.13	2.5	3	123.4	263.1	23.9	42.2	452.6
41	3.75	1.25	1.5	493	263.1	83.6	42.2	881.9
33	2.63	1	2	263.6	263.1	83.6	147.5	757.8
29	2.5	0.75	1.5	631.7	460.7	83.6	316.1	1492.2
33	2.38	1	2.5	-63.6	-75.2	83.6	147.5	92.5
49	4	2	2.25	-42.3	344.8	83.6	42.2	428.4
36	2.5	1.25	2.75	286.1	263.1	83.6	-42.2	590.6
45	2.75	2	3.75	66.7	147.2	83.6	-189.7	107.8
28	2	1.5	1.5	612.1	563.7	179.3	316.1	1671.1
50	4.13	2.75	1.5	607.9	344.8	83.6	42.2	1078.5
41	3.63	1.5	3	223.7	198.7	23.9	316.1	762.5
9	0	1	1.25	639.1	563.7	23.9	42.2	1268.8
33	2.13	1.75	2.25	618.2	563.7	-23.9	316.1	1474.1
10	0	1	1.5	569.1	460.7	179.3	316.1	1525.2
21	0	2.25	3	509.9	147.2	23.9	42.2	723.1
32	2.75	0.75	1.75	740.5	263.1	83.6	147.5	1234.8
44	3.63	1.25	2.5	-123.2	-66.5	-107.6	-189.7	-486.9
51	4	2	2.75	363.7	460.7	-107.6	42.2	759
48	3.38	2	3.25	467.5	-66.5	83.6	147.5	632.2
29	2	1.25	2	404.6	460.7	83.6	147.5	1096.5
22	0	1.25	4.25	272.2	147.2	83.6	147.5	650.6
47	3.5	2.25	2.5	296.4	198.7	179.3	316.1	990.4
52	3.63	2.5	3.25	-155	-66.5	-107.6	-189.7	-518.7
12	0	1.25	1.75	514.4	263.1	83.6	147.5	1008.6
16	0	1.75	2.25	592.4	563.7	179.3	316.1	1651.5
28	1.75	1	2.5	340.8	198.7	83.6	147.5	770.6
14	0	2	1.5	740.3	563.7	83.6	147.5	1535.2
13	0	1.75	1.5	803.2	563.7	-23.9	147.5	1490.5
10	0	1.5	1	678.9	563.7	179.3	316.1	1737.9
36	2.63	1.75	2	479	460.7	83.6	147.5	1170.9
13	0	1.5	1.75	803.2	563.7	179.3	316.1	1862.3
43	3.63	2	1.5	300.8	396.3	179.3	147.5	1023.9
35	2.38	2	2	234.5	396.3	-107.6	-189.7	333.6
39	2.63	2.25	2.25	-202.8	-75.2	83.6	-189.7	-384
33	2.25	1.25	2.5	207.3	-66.5	23.9	42.2	206.9
16	0	2	2	355.8	263.1	83.6	316.1	1018.7
42	3.5	1.5	2	235.9	147.2	-23.9	147.5	506.7
40	3.13	1.5	2.25	631.7	263.1	179.3	316.1	1390.2
30	2.13	1.5	1.75	514.4	460.7	179.3	316.1	1470.4
42	2.88	2	2.75	292.5	198.7	23.9	147.5	662.7
47	3.5	2.25	2.5	157.6	198.7	-107.6	42.2	290.8
14	0	1.75	1.75	701	396.3	179.3	147.5	1424.1
45	3.38	2.5	2	-143	147.2	23.9	42.2	70.2
43	3.13	2	2.5	481	460.7	-23.9	42.2	960
10	0	1.25	1.25	701	563.7	83.6	147.5	1495.9
19	0	1.5	3.25	416.1	396.3	179.3	316.1	1307.8
37	2.75	1.25	2.5	-59.2	-66.5	-107.6	42.2	-191.1
19	0	1.25	3.5	-216.9	147.2	-107.6	-189.7	-366.9
30	2.5	0.75	1.75	155.6	396.3	23.9	316.1	892
23	0	1.75	4	346	460.7	23.9	147.5	978.1
38	2.63	1.75	2.5	410.4	-23.7	83.6	42.2	512.6
39	2.38	1.75	3.25	213.9	198.7	83.6	316.1	812.3
42	3.38	1.25	2.5	-107.1	-75.2	83.6	147.5	48.9
32	2	1.75	2.25	582.9	396.3	83.6	316.1	1379
35	2.75	1.5	1.75	52.2	263.1	23.9	42.2	381.3
36	2.63	2	1.75	321.1	198.7	23.9	147.5	691.2
34	2.75	1.25	1.75	205.5	198.7	23.9	42.2	470.3
15	0	1.75	2	261.8	460.7	83.6	147.5	953.7

TIPI	Extravert	Agreeable	Conscienc	Stability	Openness	URICA	Group
52	11	10	13	8	10	9.1	Contempl
41	11	7	10	8	5	11	Contempl
38	3	11	7	8	9	11.6	Preparato
42	3	7	9	14	9	11.6	Preparato
49	6	9	14	14	6	10.6	Contempl
49	9	10	13	3	14	10.6	Contempl
55	11	12	8	14	10	13.3	Preparato
46	6	14	9	9	8	8.3	Contempl
53	12	12	9	8	12	10.4	Contempl
36	10	5	8	9	4	10	Contempl
55	7	13	11	13	11	8.4	Contempl
53	9	14	13	8	9	10	Contempl
56	11	6	14	14	11	11.6	Preparato
40	8	8	8	8	8	9.9	Contempl
46	8	13	10	6	9	10	Contempl
41	5	9	9	10	8	10.6	Contempl
51	7	12	12	11	9	10.7	Contempl
39	6	6	11	7	9	11.7	Preparato
37	14	2	12	5	4	8.9	Contempl
35	6	4	5	11	9	10	Contempl
30	6	8	4	2	10	11.3	Preparato
63	11	13	14	11	14	8.9	Contempl
59	10	11	14	12	12	11	Contempl
50	11	10	9	9	11	9.3	Contempl
49	7	12	9	11	10	10.3	Contempl
40	3	10	8	8	11	9.9	Contempl
52	7	8	13	10	14	11.3	Preparato
47	6	12	11	8	10	10.7	Contempl
36	6	10	7	4	9	8.9	Contempl
59	11	14	11	14	9	8.7	Contempl
40	2	8	13	5	12	9.3	Contempl
38	4	10	7	8	9	10.3	Contempl
43	13	6	8	6	10	8.3	Contempl
54	6	12	12	13	11	9.6	Contempl
60	13	13	13	7	14	12.9	Preparato
51	8	12	12	8	11	11.6	Preparato
41	7	14	5	10	5	10.4	Contempl
51	8	14	11	8	10	12.1	Preparato
21	3	7	3	4	4	10.1	Contempl
52	10	13	9	10	10	9.3	Contempl
42	8	11	8	9	6	11.4	Preparato
40	4	12	11	4	9	10.3	Contempl
37	7	10	7	5	8	9.4	Contempl
42	5	10	9	8	10	11	Contempl
43	10	10	7	8	8	10.4	Contempl
46	14	8	9	7	8	9.9	Contempl
48	11	8	11	5	13	10.1	Contempl
48	12	12	5	7	12	11.6	Preparato
46	12	8	7	9	10	7.9	Preconten
50	6	8	14	10	12	7.7	Preconten
47	8	9	14	8	8	11.7	Preparato
42	7	10	11	5	9	8.1	Contempl
48	7	13	6	8	14	7.7	Preconten
50	10	11	12	6	11	10	Contempl
51	13	9	8	11	10	11.9	Preparato
54	12	13	11	7	11	8	Preconten
55	13	8	14	12	8	14	Preparato
24	2	10	6	2	4	9.6	Contempl
25	6	2	8	6	3	9.9	Contempl
51	14	5	13	8	11	10.1	Contempl
49	14	7	10	9	9	8.9	Contempl
44	8	9	9	7	11	12.7	Preparato
28	6	8	7	2	5	10.4	Contempl
46	12	10	7	7	10	8.9	Contempl

40	6	12	8	3	11	6.9	Preconten
43	9	10	4	12	8	12	Preparato
42	11	8	6	8	9	10.3	Contempl
52	10	14	11	8	9	9.1	Contempl
30	6	6	2	5	11	11.7	Preparato
43	6	11	9	8	9	9.4	Contempl
40	6	10	12	8	4	10.7	Contempl
55	6	11	12	13	13	11.3	Preparato
42	7	10	8	6	11	9.1	Contempl
52	9	10	12	9	12	11.9	Preparato
62	13	13	14	9	13	11.1	Preparato
51	7	12	9	14	9	10.1	Contempl
50	12	10	9	8	11	11	Contempl
41	10	11	4	8	8	9.6	Contempl
39	6	3	9	14	7	10.3	Contempl
34	4	3	11	10	6	13.4	Preparato
52	14	8	12	5	13	11.6	Preparato
51	6	13	12	9	11	10.7	Contempl
48	5	11	11	12	9	10.6	Contempl
41	5	10	11	7	8	7.9	Preconten
49	8	14	10	5	12	9.3	Contempl
36	8	7	8	4	9	10.1	Contempl
50	7	14	8	12	9	10.4	Contempl
67	11	14	14	14	14	8.7	Contempl
50	10	9	14	7	10	14	Preparato
46	10	8	14	6	8	8.4	Contempl
46	6	10	12	12	6	10.3	Contempl
45	7	12	9	8	9	10.4	Contempl
37	5	13	7	4	8	10.6	Contempl
59	10	14	11	11	13	12.3	Preparato
49	8	9	11	9	12	10.7	Contempl
36	9	9	5	3	10	10	Contempl
55	11	12	11	12	9	8.6	Contempl
40	11	9	8	3	9	11	Contempl
41	8	11	9	7	6	12.7	Preparato
25	4	9	4	4	4	9.7	Contempl
47	5	10	12	8	12	13.7	Preparato
31	2	8	5	8	8	12.1	Preparato
36	10	9	8	2	7	7.9	Preconten
51	11	3	14	10	13	10.7	Contempl
53	9	11	12	9	12	11.4	Preparato
58	12	14	12	9	11	10.9	Contempl
22	4	6	6	2	4	9.9	Contempl
57	10	13	14	8	12	7.9	Preconten
48	7	11	12	4	14	8.7	Contempl
39	8	9	9	6	7	12	Preparato
47	11	7	12	6	11	10.4	Contempl
40	14	2	2	8	14	9.3	Contempl
32	3	14	2	2	11	11	Contempl
57	11	11	7	14	14	10.3	Contempl
47	3	12	13	12	7	9.9	Contempl
56	13	12	9	13	9	10.1	Contempl
46	13	13	7	5	8	11.3	Preparato
64	11	12	14	14	13	8.9	Contempl
43	10	8	11	10	4	9.6	Contempl
48	9	11	11	5	12	9.6	Contempl
43	8	13	4	10	8	11.3	Preparato
63	8	14	13	14	14	10.4	Contempl
44	6	11	10	9	8	12.4	Preparato
47	5	12	9	12	9	7.3	Preconten
41	6	9	11	5	10	9	Contempl
55	7	12	12	12	12	9	Contempl
40	9	11	7	5	8	8.3	Contempl
42	11	9	3	7	12	11	Contempl
33	4	8	11	4	6	10.7	Contempl

etoh	Smoking	BP Med	DM Med	Social	Pattern	OpDate	Type	OpBW	OpBMI
1	current	no	No	unskilled	shifts	09.03.11	bypass	136	52.5
0	never	yes	Yes	Retired	N/A	01.06.11	sleeve	149	46
0	never	yes	No	Unemploy	N/A	06.06.11	bypass	126	52.4
10	stopped	yes	Yes	mangerial	no	04.04.11	band	126.7	42.3
0	never	no	No	professior	no		Declined/ refused surgery		
21	never	yes	No	professior	no		Declined/ refused surgery		
0	current	yes	No	Unemploy	N/A		Declined/ refused surgery		
0	never	yes	No	Retired	N/A		Declined/ refused surgery		
0	never	no	Yes	Unemploy	N/A		Declined/ refused surgery		
0	stopped	no	Yes	Unemploy	N/A	19.03.12	sleeve	136.9	46.8
28	stopped	yes	Yes	skilled - m	no	06.07.10	bypass	145	45.3
0	never	no	No	professior	shifts	02.07.11	bypass	104	36.4
0	current	no	No	professior	shifts		Declined/ refused surgery		
2	never	no	No	skilled - m	no	29.11.10	bypass	144.2	41.2
0	never	no	Yes	Unemploy	N/A	20.12.10	bypass	154	56.6
0	current	no	Yes	Unemploy	N/A	18.11.10	bypass	144.7	41.8
0	stopped	no	No	Retired	N/A	09.05.11	band	111.6	47.1
0	never	no	No	Unemploy	N/A	13.06.11	bypass	147	55.3
0	never	no	No	unskilled	shifts	18.07.11	bypass	153.4	47.3
0	stopped	yes	No	Unemploy	N/A		Declined/ refused surgery		
0	current	no	No	Unemploy	N/A	24.02.11	bypass	130	50.2
0	current	yes	Yes	Retired	N/A		Declined/ refused surgery		
0	never	no	No	mangerial	no	10.08.11	bypass	92	38.8
0	current	yes	Yes	Unemploy	N/A		Declined/ refused surgery		
15	never	yes	No	partly skil	no	23.05.12	bypass	160.4	49
0	current	yes	No	Retired	N/A		Declined/ refused surgery		
0	never	no	No	professior	no	15.12.10	bypass	112	44.3
0	never	no	No	professior	no	15.03.11	bypass	129.6	50.6
0	stopped	no	No	Unemploy	N/A		Declined/ refused surgery		
12	never	no	No	professior	no	17.01.12	band	106	39.4
0	current	no	Yes	unskilled	no	05.04.11	bypass	125.7	46.7
0	never	yes	No	skilled - m	no	21.12.10	bypass	152.2	47
0	never	no	No	skilled - n	no		Declined/ refused surgery		
0	stopped	no	Yes	Unemploy	N/A	23.05.11	bypass	160.8	44.1
0	never	no	No	skilled - n	no		Declined/ refused surgery		
5	current	yes	Yes	Unemploy	N/A	15.02.12	sleeve	168.2	63.3
0	current	no	No	professior	no	12.05.11	bypass	156.2	61
0	never	yes	Yes	skilled - m	shifts	24.05.11	bypass	150.3	56.6
0	current	yes	Yes	Unemploy	N/A	25.08.11	bypass	113.3	41.1
0	stopped	no	No	Unemploy	N/A	22.08.11	bypass	161	55.7
0	current	no	No	unskilled	no	05.10.11	bypass	180.6	61.8
0	never	no	No	Student	no	05.09.11	bypass	167	62.1
0	never	no	No	skilled - n	shifts	13.04.11	bypass	151	52.9
0	never	yes	No	unskilled	shifts		Declined/ refused surgery		
0	current	no	No	Unemploy	N/A	17.04.12	sleeve	139.4	57.3
0	current	no	No	unskilled	shifts		Declined/ refused surgery		
0	stopped	no	No	mangerial	no	08.12.10	bypass	143.2	62
0	never	yes	No	Retired	N/A	05.05.11	bypass	132.7	48.7
10	stopped	no	No	Unemploy	N/A	26.05.11	bypass	149.8	52.4
0	stopped	yes	Yes	Retired	N/A	29.10.12	bypass	125.9	48.6
10	never	yes	No	unskilled	shifts	04.10.11	bypass	145.3	56.8
0	never	no	Yes	mangerial	shifts		Declined/ refused surgery		
0	stopped	yes	Yes	Retired	N/A	10.08.11	sleeve	128.3	50.1
0	never	no	No	Unemploy	N/A	18.10.12	bypass	126.3	47.5
0	never	no	No	mangerial	no	04.12.12	bypass	130.6	51
0	stopped	no	No	skilled - n	no	18.07.11	bypass	185.2	61.9
0	stopped	no	No	skilled - n	no		Declined/ refused surgery		
0	never	no	Yes	Unemploy	N/A	17.08.11	bypass	138.9	52.3
30	current	no	No	Unemploy	N/A	16.10.12	bypass	140.3	56.2
0	never	no	No	Unemploy	N/A	17.05.11	bypass	163.7	56.6
0	current	no	No	Unemploy	N/A	14.12.11	bypass	114.6	42.1
8	stopped	yes	No	skilled - m	no		Declined/ refused surgery		
0	current	no	No	skilled - n	no	29.06.11	bypass	119.8	44
0	current	no	No	Unemploy	N/A	08.06.11	sleeve	109.2	44.9

0	stopped	yes	No	mangerial	no	09.03.11	bypass	121.9	43.7
14	never	yes	No	partly skil	no	25.05.11	sleeve	113.8	42.3
8	stopped	no	Yes	skilled - n	no	05.10.11	bypass	150.1	54.5
0	stopped	no	Yes	unskilled	no	22.03.11	bypass	96.8	38.3
0	current	no	No	Unemploy	N/A	19.05.11	bypass	133.1	48.9
0	never	no	No	partly skil	shifts	31.05.11	bypass	109.1	39.1
0	current	no	No	mangerial	no	20.06.11	bypass	163	59.9
0	never	no	No	skilled - n	no	20.05.11	sleeve	116	41.6
0	never	no	No	partly skil	no	04.07.11	bypass	125.5	50.3
0	never	no	No	Unemploy	N/A		Declined/ refused surgery		
0	stopped	yes	No	Retired	N/A		other		
0	never	no	No	skilled - n	no	27.06.11	bypass	140	52.1
0	stopped	no	No	partly skil	no	22.06.11	bypass	129.7	47.1
0	current	no	No	Unemploy	N/A	28.05.11	bypass	101.9	45.3
0	stopped	yes	No	skilled - m	no	07.07.11	sleeve	124.6	38.5
16	never	yes	No	skilled - n	no		Declined/ refused surgery		
0	current	no	No	unskilled	shifts	17.10.11	sleeve	145	49
20	stopped	no	No	unskilled	no	14.09.11	sleeve	132.3	52.3
12	never	no	No	Unemploy	N/A		Declined/ refused surgery		
0	never	yes	Yes	partly skil	shifts	06.08.12	bypass	178.4	68
0	stopped	no	No	Unemploy	N/A	08.06.11	bypass	163.3	60
0	stopped	no	No	Retired	N/A	01.05.12	bypass	148.4	47.4
0	never	no	No	unskilled	no		Declined/ refused surgery		
0	never	yes	No	unskilled	no	15.08.11	bypass	124.3	48.6
0	stopped	no	No	unskilled	no	12.07.11	bypass	144.9	55.2
0	stopped	no	No	unskilled	no	13.10.11	bypass	105.7	42.9
4	never	yes	No	skilled - n	no	21.11.11	bypass	153.3	50.1
0	current	yes	Yes	Unemploy	N/A	05.03.12	bypass	133	46
0	never	no	No	Unemploy	N/A	20.10.11	bypass	170.9	52.7
0	never	no	No	mangerial	no	02.07.12	bypass	189.5	59.1
0	never	no	No	Unemploy	N/A		Declined/ refused surgery		
0	stopped	no	No	Unemploy	N/A	03.07.12	sleeve	156.9	58.3
10	never	no	No	skilled - n	shifts	03.11.11	bypass	148.3	54.5
0	current	yes	Yes	Retired	N/A	08.02.12	sleeve	125	47
0	stopped	yes	Yes	Retired	N/A		Declined/ refused surgery		
0	current	no	No	Unemploy	N/A	27.06.11	bypass	156.1	50.1
4	current	no	No	partly skil	no	17.10.11	bypass	138	50.7
2	stopped	yes	Yes	Retired	N/A		Declined/ refused surgery		
0	never	no	No	mangerial	no	16.01.12	bypass	127.5	47.4
0	never	no	No	professior	no	12.09.11	bypass	122.1	48.3
0	stopped	no	No	partly skil	no	28.09.11	bypass	136.4	56
0	never	no	No	skilled - n	no	22.08.12	sleeve	231.8	83.1
25	never	no	Yes	Retired	N/A		Declined/ refused surgery		
0	never	yes	No	professior	no		Declined/ refused surgery		
0	never	no	No	Retired	N/A		Declined/ refused surgery		
5	stopped	yes	Yes	mangerial	no	19.10.11	bypass	133	45
0	stopped	no	No	unskilled	shifts	16.01.12	bypass	164	51.2
0	current	yes	No	professior	no	20.04.11	bypass	152	44.4
0	never	yes	No	Retired	N/A	11.06.12	bypass	140.4	53.5
5	never	no	No	skilled - n	shifts	14.11.11	bypass	175	49
0	stopped	yes	No	partly skil	no	21.11.11	bypass	108.5	38.9
5	stopped	yes	No	Retired	N/A	19.03.12	bypass	218	74.6
0	stopped	no	No	Unemploy	N/A	10.04.12	sleeve	140	52.7
30	stopped	yes	Yes	unskilled	no	16.11.11	bypass	161	53.2
0	stopped	yes	No	Retired	N/A		Declined/ refused surgery		
0	stopped	no	No	mangerial	no	26.11.12	bypass	169.2	55.2
0	current	no	No	Unemploy	N/A	07.12.11	bypass	155.9	63.2
2	current	yes	No	skilled - m	no		Declined/ refused surgery		
0	current	no	No	skilled - n	shifts		Declined/ refused surgery		
0	never	no	No	unskilled	no	30.11.11	bypass	132.9	50.6
0	current	no	Yes	Unemploy	N/A		Declined/ refused surgery		
0	never	no	Yes	skilled - m	no	09.07.12	bypass	85.8	36.7
15	never	yes	No	unskilled	no	20.11.12	bypass	153.2	53
0	current	yes	No	professior	no		Declined/ refused surgery		
0	current	yes	No	Unemploy	N/A	28.09.11	bypass	200.3	68.5

IHD	BP	OSA	COPD/Ast	DM	PCOS	Psych	Abuse	Other	Comorb
no	no	no	no	No	no	yes	no	Musculosk	2
no	yes	no	no	Yes	no	yes	no	None	3
no	no	no	yes	No	no	no	no	None	1
yes	yes	no	no	Yes	no	no	no	None	3
no	no	no	no	No	no	no	no	Musculosk	1
no	yes	no	no	No	no	yes	no	None	2
yes	yes	no	yes	Yes	no	no	no	CVA/TIA	6
no	yes	no	no	No	no	no	no	None	1
no	yes	no	no	Yes	no	yes	no	None	3
no	no	no	no	Yes	no	no	no	Thyroid	4
no	yes	no	no	Yes	no	no	no	Musculosk	3
no	no	no	no	No	yes	yes	yes	None	3
no	no	no	no	No	no	no	no	Musculosk	1
no	no	no	no	No	no	no	no	Musculosk	1
no	no	no	no	Yes	no	no	yes	Musculosk	3
no	no	no	no	Yes	no	yes	no	None	2
no	no	yes	yes	No	no	yes	yes	None	4
no	no	no	no	No	no	no	no	None	0
no	no	no	no	No	no	no	no	Musculosk	1
no	no	no	no	No	no	yes	no	Musculosk	2
no	no	no	no	No	no	yes	no	None	1
no	yes	yes	no	Yes	no	no	no	Musculosk	4
no	no	no	yes	No	no	no	yes	Musculosk	3
no	yes	yes	yes	Yes	no	yes	no	Musculosk	6
no	yes	no	no	No	no	no	no	None	1
no	yes	no	yes	No	no	no	no	None	2
no	no	no	yes	No	no	no	no	None	1
no	no	no	no	No	no	no	no	None	0
no	no	no	no	No	no	yes	no	Thyroid	4
no	no	no	no	No	no	no	no	Thyroid	3
no	no	no	no	Yes	no	yes	no	Musculosk	3
no	yes	no	no	No	no	no	no	None	1
no	no	no	no	No	no	no	no	Musculosk	1
no	no	yes	no	Yes	no	yes	no	None	3
no	no	no	yes	No	no	no	no	Musculosk	2
no	yes	no	no	Yes	no	yes	yes	None	4
no	no	no	no	No	no	no	no	None	0
no	yes	no	yes	Yes	yes	yes	no	None	5
no	yes	no	yes	Yes	no	yes	no	None	4
no	no	no	no	No	no	no	no	Musculosk	1
no	no	no	no	No	no	no	no	None	0
no	no	no	no	No	no	yes	no	Thyroid	4
no	no	no	no	No	no	yes	no	Musculosk	2
no	yes	no	yes	Yes	no	no	no	Musculosk	4
no	no	no	no	Yes	no	yes	no	Musculosk	3
no	no	no	yes	Yes	no	yes	yes	Musculosk	5
no	no	no	no	No	no	no	yes	None	1
no	yes	yes	no	No	no	yes	no	None	3
no	no	no	yes	Yes	no	no	no	Musculosk	3
no	yes	yes	yes	Yes	no	yes	no	Musculosk	6
no	yes	no	no	No	no	yes	no	Musculosk	3
no	yes	yes	no	Yes	no	yes	no	None	4
no	yes	yes	yes	Yes	no	yes	no	Musculosk	6
no	no	no	no	No	no	yes	no	Musculosk	2
no	no	no	yes	No	no	no	no	None	1
no	no	no	no	No	no	yes	no	None	1
no	no	no	no	No	no	yes	no	None	1
no	no	no	no	Yes	yes	yes	no	None	3
no	no	no	yes	No	no	yes	no	None	2
no	no	no	no	No	no	no	no	None	0
no	no	no	no	No	no	yes	yes	Musculosk	3
no	yes	no	no	No	no	no	no	Musculosk	2
no	no	yes	no	No	no	yes	no	None	2
no	no	no	no	Yes	no	yes	no	Musculosk	3

no	yes	no	yes	Yes	no	yes	no	None	4
no	yes	no	no	No	no	no	no	None	1
no	yes	no	no	Yes	no	no	no	Musculosk	3
no	no	no	no	Yes	no	no	no	None	1
no	no	no	no	No	no	yes	yes	None	2
no	no	no	yes	Yes	no	no	no	Musculosk	3
no	no	no	yes	No	no	no	no	Musculosk	2
no	no	no	no	No	no	no	no	None	0
no	no	no	no	No	no	yes	no	Musculosk	2
no	no	no	yes	No	yes	yes	no	None	3
no	yes	no	no	No	no	yes	no	Musculosk	3
no	no	no	no	No	no	no	no	Musculosk	1
no	no	no	no	No	no	yes	no	None	1
no	no	yes	no	No	no	yes	yes	None	3
no	yes	no	no	No	no	yes	no	None	2
no	no	no	no	No	no	yes	yes	None	2
no	no	no	no	No	no	yes	no	None	1
no	no	no	no	No	no	no	no	None	0
no	no	no	no	No	no	yes	no	Musculosk	2
no	yes	no	yes	Yes	no	yes	no	Musculosk	5
no	no	no	no	No	no	yes	no	Musculosk	2
no	no	no	no	Yes	no	no	no	Musculosk	2
no	no	no	no	No	no	no	no	Musculosk	1
no	yes	no	no	No	no	yes	no	Musculosk	3
no	no	no	yes	No	no	yes	no	Musculosk	3
no	no	no	no	No	no	no	no	Musculosk	1
no	yes	yes	no	No	no	no	no	Musculosk	3
no	yes	no	no	Yes	no	no	yes	Musculosk	4
no	no	no	no	No	no	yes	no	Musculosk	2
no	no	no	no	No	no	no	no	None	0
no	no	no	no	No	no	no	no	Multiple S	4
no	no	no	no	No	no	yes	no	Musculosk	2
no	no	no	no	No	no	no	no	None	0
no	yes	no	yes	Yes	no	yes	no	Musculosk	5
no	yes	no	yes	Yes	no	yes	no	Musculosk	5
no	no	no	no	No	no	yes	no	Musculosk	2
no	no	no	yes	No	no	no	no	None	1
no	yes	yes	yes	Yes	no	yes	no	Musculosk	6
no	no	no	no	No	no	yes	no	None	1
no	no	no	no	No	no	no	no	None	0
no	no	no	no	No	yes	no	no	None	1
no	no	yes	no	No	no	no	yes	None	2
no	no	yes	no	Yes	no	yes	no	Thyroid	6
no	yes	no	no	No	no	yes	yes	Thyroid	6
no	no	no	no	No	no	yes	no	Musculosk	2
yes	yes	yes	no	Yes	no	yes	no	Musculosk	6
no	no	no	yes	No	no	no	no	None	1
no	yes	no	no	No	no	yes	no	None	2
no	yes	no	no	No	no	yes	no	Musculosk	3
no	no	no	no	No	no	no	no	None	0
no	yes	no	no	Yes	no	no	no	None	2
no	yes	no	no	No	no	yes	no	Musculosk	3
no	no	no	no	No	no	yes	no	Musculosk	2
no	yes	no	no	Yes	no	no	no	Musculosk	3
yes	yes	yes	yes	Yes	no	no	no	Musculosk	6
no	yes	no	no	No	no	yes	no	None	2
no	no	no	no	No	no	yes	yes	None	2
no	yes	yes	no	No	no	no	no	None	2
no	no	no	no	No	no	yes	no	Thyroid	4
no	no	no	yes	No	no	yes	no	Musculosk	3
no	no	no	no	Yes	no	no	no	Musculosk	2
no	no	yes	no	Yes	no	no	no	None	2
no	yes	yes	yes	No	no	yes	no	Musculosk	5
no	yes	no	yes	No	no	no	no	None	2
no	yes	no	no	No	no	yes	yes	None	3

FU Date	Duration	FU BW	FU BMI	%eBMI Lo	FUHbA1c	FU Syst	FU Diast	BPMedSto	DMMedSt
12.04.12	400	100.4	38.7	50				N/A	N/A
31.05.12	365	104.7	32.3	65.1					
									N/A
26.04.12	388	103.4	34.5	44.9					
								N/A	N/A
									N/A
									N/A
									N/A
								N/A	
								N/A	
21.10.11	472	118	36.8	41.6		136	78	no	Yes
31.07.12	395	59.6	20.9	136.2				N/A	N/A
								N/A	N/A
07.09.11	282	109	31.2	62				N/A	N/A
13.12.11	358	86.6	31.8	78.4	47.5			N/A	Yes
05.03.13	838	83	24	106	30.1			N/A	Yes
12.06.12	400	93.3	39.3	35				N/A	N/A
07.01.13	574	84.4	31.8	77.7				N/A	N/A
21.03.13	612	88.4	27.3	89.8				N/A	N/A
									N/A
19.03.13	754	108.2	41.7	33.4				N/A	N/A
24.05.12	288	75.5	31.8	50.4				N/A	N/A
18.04.13	330	120.8	36.9	50.4		132	70	no	N/A
									N/A
16.02.12	428	77.2	30.5	71.3				N/A	N/A
13.02.12	335	90.3	35.3	59.9				N/A	N/A
								N/A	N/A
10.01.13	359	106	39.4	0				N/A	N/A
12.09.12	526	83	30.9	73	42.1			N/A	Yes
05.09.11	258	101	31.2	71.9		140	96	yes	N/A
								N/A	N/A
23.05.12	366	128.7	35.3	46.1	32.2	130	76	N/A	Yes
								N/A	N/A
22.11.12	281	129.6	48.8	37.9					
02.05.12	356	100.6	39.3	60.3				N/A	N/A
05.05.12	347	112.3	42.3	45.3	46.4	112	78	no	Yes
20.01.13	514	85	30.8	63.7	45.4	120	80	no	No
11.12.12	477	92.4	32	77.3				N/A	N/A
12.07.12	281	117.5	40.2	58.7				N/A	N/A
19.01.12	136	122.5	45.5	44.6				N/A	N/A
23.12.12	620	104.7	36.7	58.2		109	58	N/A	N/A
									N/A
08.02.13	297	124.4	51.1	19.1				N/A	N/A
								N/A	N/A
13.01.12	401	99.6	43.1	51				N/A	N/A
20.04.12	351	87.3	32.1	70.2		108	66	no	N/A
23.07.12	424	87.1	30.5	80				N/A	N/A
12.11.12	14	98.6	38	44.7					
22.10.12	384	93.2	36.4	64.1		107	57	yes	N/A
								N/A	
05.07.12	330	91.3	35.7	57.5					
10.12.12	53	107.1	40.3	32.1				N/A	N/A
								N/A	N/A
18.05.12	305	120.5	40.3	58.6		115	78	N/A	N/A
								N/A	N/A
31.05.12	288	91.1	34.3	66	33.3			N/A	Yes
13.02.13	120	115.4	46.2	32				N/A	N/A
								N/A	N/A
07.02.13	421	61.2	22.5	114.7				N/A	N/A
									N/A
19.03.13	629	87.8	32.2	61.9		132	75	N/A	N/A
25.05.12	352							N/A	N/A

									N/A
04.05.12	345	76.9	28.6	79.3					N/A
30.08.12	330	103	37.4	58	36.6			N/A	No
09.03.12	353	65.3	25.8	93.8	47.5	128	74	N/A	Yes
04.03.13	655	82.1	30.2	78.4				N/A	N/A
19.06.12	385	80.8	29	71.9				N/A	N/A
17.07.12	393	117.8	43.3	47.6				N/A	N/A
01.05.12	347	78.6	28.2	80.8				N/A	N/A
03.04.12	274	95.2	38.1	48				N/A	N/A
								N/A	N/A
									N/A
22.05.12	330	92.8	34.5	64.9				N/A	N/A
24.05.12	337	103.5	37.6	43.1				N/A	N/A
12.03.12	289	69.9	31.1	70.1				N/A	N/A
11.06.12	340	102.7	31.7	50.2					N/A
									N/A
06.03.12	141	120.3	40.7	34.8				N/A	N/A
28.06.12	288	92.9	36.7	57				N/A	N/A
								N/A	N/A
19.03.13	225	119	45.3	52.7	60.7	120	70	yes	Yes
12.03.12	278	120.9	44.4	44.5				N/A	N/A
19.11.12	202	96	30.6	74.8		126	80	N/A	N/A
								N/A	N/A
18.05.12	277	80.4	31.4	72.8		177	87	yes	N/A
13.08.12	398	105.2	40.1	50.1		128	65	N/A	N/A
07.12.12	421	70.3	28.5	80.3				N/A	N/A
06.02.13	443	99	32.3	70.8		127	71	no	N/A
05.02.13	337	81.4	28.2	84.9	42.1	120	80	no	No
26.04.13	554	101.4	31.3	77.3		130	60	N/A	N/A
23.08.12	52	161.2	50.3	25.9				N/A	N/A
								N/A	N/A
04.02.13	216	120.8	44.9	40.3				N/A	N/A
21.12.12	414	86.2	31.7	77.4				N/A	N/A
14.12.12	310	93.6	35.2	53.6					
03.07.12	372	102.6	32.9	68.4				N/A	N/A
23.10.12	372	71.8	26.4	94.7				N/A	N/A
02.04.13	442	78.6	29.2	81.1				N/A	N/A
29.05.12	260	87.2	34.5	59.3				N/A	N/A
09.07.12	285	93.8	38.5	56.4				N/A	N/A
15.10.12	54	130.4	46.8	62.6				N/A	N/A
								N/A	
									N/A
								N/A	N/A
14.03.13	423	106.7	33.3	68.3				N/A	N/A
12.07.12	449	100.9	29.5	76.9					N/A
28.01.13	231	108.8	41.5	42.3					N/A
17.07.12	246	124	34.7	59.5				N/A	N/A
03.12.12	378	74.3	26.6	88.2		121	82	yes	N/A
15.04.13	392	168	57.5	34.5		140	70	no	N/A
06.09.12	149	110.9	41.7	39.6				N/A	N/A
14.12.12	394	104.3	34.4	66.5	32.2			no	Yes
									N/A
								N/A	N/A
14.09.12	282	103.1	41.8	56		113	59	N/A	N/A
									N/A
								N/A	N/A
22.02.13	450	83	31.6	74.2				N/A	N/A
								N/A	
04.03.13	238	68.9	29.4	62	34.4			N/A	Yes
									N/A
									N/A
31.08.12	338	133	45.5	52.9		109	68	yes	N/A

Abbreviations

WHO	World Health Organisation
BMI	Body Mass Index
BF%	Body Fat Percentage
DEXA	Dual energy x-ray absorptiometry
BIA	Bioelectrical impedance analysis
MRI	Magnetic Resonance Imaging
USS	Ultrasound Scan
NHS	National Health Service
T2DM	Type 2 Diabetes Mellitus
IHD	Ischaemic Heart Disease
UK	United Kingdom
LCD	Low calorie diet
VLCD	Very low calorie diet
RYGBP	Roux-en-Y Gastric Bypass
DM	Diabetes Mellitus
HbA1c	Glycosylated haemoglobin
CT	Computed Tomography
CI	Confidence Interval
IOTF	International Obesity Task Force
PCP	Primary Care Physician
FFA	Free Fatty-Acid
QoL	Quality of Life
OR	Odds Ratio
NICE	National Institute of Clinical Excellence
BPD	Biliopancreatic Diversion
CART	Classification And Regression Tree
eBMI	Excess BMI
BP	Blood Pressure
BAROS	Bariatric Analysis and Reporting Outcome System
BW	Bodyweight
eBWL	Excess Bodyweight Loss
AOR	Adjusted Odds Ratio
BED	Binge Eating Disorder

MMPI	Minnesota Multiphasic Personality Inventory
HOMA-DI	Homeostatic Model of Assessment estimated glucose Disposition Index
LADA	Latent Autoimmune Diabetes of the Adult
HOMA-IR	Homeostatic Model of Assessment estimated Insulin Resistance
GLP-1	Glucagon-like Peptide 1
SNS	Sympathetic Nervous System
RAAS	Renin-Angiotensin-Aldosterone System
HPA	Hypothalamic-Pituitary Axis
TFEQ	Three Factor Eating Questionnaire R-18
BPAQ	Baecke Physical Activity Questionnaire
OSQoL	Obese Specific Quality of Life
TIPI	Ten Item Personality Inventory (TIPI)
URICA	University of Rhode Island Change Assessment
PCT	Primary Care Trust
SD	Standard Deviation
SG	Study Group
EG	Exclusion Group
BOSPA	British Obesity Surgery Patients Association
CPAP	Continuous Positive Airway Pressure