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Pharmacotherapy and weight management: efficacy and clinical effectiveness in patients with obesity and type 2 diabetes

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Thesis is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in Clinical Pharmacology and Therapeutics

Institute of Cardiovascular and Medical Sciences

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Abstract

The prevalence of obesity worldwide has more than doubled since 1980. The World Health Organisation (WHO) estimates that more than one in ten adults in the global population is obese. Cardiovascular and metabolic health can be improved with moderate weight loss; losses of 5%–10% have been found to improve conditions such as diabetes, hypertension and cholesterol and low-density lipoprotein (LDL) levels. Within the UK, a number of weight management programmes that depend on lifestyle intervention (tier 2) and others that supplement this with drug therapy (tier 3) and surgery (tier 4) are available.

The guidelines produced by the Scottish Intercollegiate Guideline Network (SIGN) advocate that weight management programmes address changes to diet, physical activity and behaviour. For patients with a body mass index (BMI) $\geq$30 kg/m^2 or $\geq$28 kg/m^2 in patients with comorbidities, orlistat can be considered as a drug intervention on a case-by-case basis following a full risk and benefit assessment. The objective of the Glasgow and Clyde Weight Management Service (GCWMS), a specialist weight-loss programme, is for patients to lose at least 5 kg.

There are a number of metabolic disorders that are associated with obesity. One such disorder is type 2 diabetes mellitus, where weight loss is a standard recommendation to improve blood glucose control. Randomised controlled trials (RCTs) of orlistat indicate that the drug is effective in promoting weight loss and improving metabolic control for those patients with the comorbidity of type 2 diabetes and obesity. There are several different groups of anti-diabetic drugs that can be used to manage diabetes. The effects of the different medications on body weight are considerable. Some, such as biguanides (metformin), dipeptidyl peptidase-4 inhibitors (DPP-IV), Glucagon-like peptide-1 agonist (GLP-1) and sodium-glucose co-transporter-2 inhibitors (SGLT2), either have no effect on weight or can cause weight loss. Others, such as sulfonylureas (SUs) and thiazolidinediones (TZDs) can lead to weight gain.

This thesis explores the impact of lifestyle interventions in weight management services, and the impact of drug interventions, on weight loss and glycaemic control. It is supported by the results of five complementary studies that reviewed the effect of orlistat on type 2 diabetes and assessed the impact of the prescription patterns of anti-diabetic drugs in addition to the effects of these pharmacological interventions on weight change in comorbid patients.

The first aim of this thesis is to review the evidence of the effects of orlistat on diabetic outcomes. The second aim is to evaluate the lifestyle interventions, and phase 2 of the GCWMS. Finally, the third aim is to determine the prescribing patterns of anti-diabetic drugs, and to observe the association between anti-diabetic medications and weight change. This thesis addresses the following objectives:

1. To undertake a systematic review and meta-analysis of published studies in order to review the evidence of the effects of orlistat on weight loss, specifically concerning glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG), using the Cochrane review methodology;
2. To investigate the proportion of patients losing 5 kg of weight, commencing from their entry into the GCWMS programme, until the end of the lifestyle phase of treatment, for individuals of different ages, genders, and socioeconomic groups;
3. To study the proportion of patients losing 5 kg of weight, commencing from their entry into the GCWMS programme, until the end of phase 2, with the three different interventions of orlistat, low-calorie diet (LDL), and further weight loss (FWL);
4. To investigate the proportion of patients referred to the GCWMS on weight-neutral, mixed, and weight-gaining anti-diabetic medications;
5. To investigate the effect of baseline anti-diabetic medications on weight change for patients within a weight management programme.

Chapter 2 presents the first study, which was a systemic review that considered the evidence collected in RCTs on the efficacy of orlistat for type 2 diabetes and weight loss. The effects were considered at the biochemical level and included the levels of glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) in people with overweight and obesity. The results, collected from 2,802 participants in 12 trials, were combined into a meta-analysis. The overall finding was that a combination of orlistat and lifestyle intervention yielded superior results. When the results were compared, it was evident that patients who are overweight or obese who were subjected to combined lifestyle and drug intervention lost more weight and had better glycaemic control than patients who were subjected to lifestyle interventions only.

Chapter 3 presents the second study which appraised the effectiveness of a real-life NHS lifestyle weight management intervention in reducing body weight by ≥5 kg. The study followed 23,650 patients referred to the GCWMS, of whom 7,329 attended at least two lifestyle intervention sessions. Those individuals had either a BMI of ≥30 kg/m^2, with

obesity-related comorbidities, or a BMI of ≥35 kg/m2 and were aged ≥18 years. The lifestyle interventions included a combination of a 600 kcal deficit diet, exercise, and behavioural changes. 30% of the overall group succeeded in losing ≥5 kg. Out of those who completed the programme, however, a considerably higher number (46%) lost ≥5 kg. The greatest losers were men, those aged ≥40 years, those with a BMI ≥50 kg/m^2, and those from areas that are more affluent.

Chapter 4 presents the third study which focused on patients who lost ≥5 kg in phase 2 of the treatment provided by GCWMS which comprised a low-calorie diet (LCD), orlistat 120 mg, three times a day, or further weight loss (FWL). Participants on LCD were prescribed a 1,200 or 1,500 calorie plan; however, those on FWL repeated the lifestyle phase. There were 3,262 participants who attended at least two sessions in phase 2; these were divided into three categories: 536 who took orlistat, 1,043 who followed a LCD and 1,683 who were selected FWL. By the end of phase 2, the levels of success in terms of weight loss across the groups varied from 31% of participants in the orlistat group to 22% of participants in the LCD group and 83% of participants in the FWL group who lost ≥5 kg.

Chapter 5 presents the fourth study, which evaluated the pattern of anti-diabetic drug prescriptions for comorbid patients referred to the GCWMS. The study also looked at the proportion of patients who were referred prior to and after the publication of updated SIGN guidelines for the prescription of anti-diabetic medication. In total, the study enrolled 3,063 participants who received anti-diabetic medications, of whom 47.8% received weight-neutral medications, 39.4% had mixed-effect medications and 12.7% took weight-gaining drugs. Prior to the publication of the SIGN guidelines, 11.6% of participants were on weight-gaining drugs, a proportion that did not change significantly one year after the release of the guidelines. Weight-neutral drugs were more commonly prescribed to women, those with a higher BMI and young people. No relationship was observed between the Scottish Index of Multiple Deprivation (SIMD) and anti-diabetic drug prescriptions. Weight-gaining drugs such as SUs and TZDs were more commonly prescribed to older patients and those with lower BMIs.

Chapter 6 presents the fifth and final study, which investigated the effect on body weight of anti-diabetic medications in 998 participants following the lifestyle phase of the GCWMS. By the end of the programme, patients who were on weight-neutral anti-diabetic drugs achieved a mean weight change of -3.3 kg (95% confidence interval [CI]: -3.8 to -2.9

kg) and those on weight-gaining drugs achieved a mean weight change of -2.5 kg (95% CI: -3.2 to -1.8 kg), p =0.05. Among those who completed the programme, the difference was statistically significant (p =0.005). The association between weight change and anti-diabetic drug type was not explained by differences in sex, initial BMI or age.

To conclude, there was a clinically and statistically significant change in weight, HbA1c and FPG in patients with obesity and type 2 diabetes who used orlistat. Of the patients following the GCWMS lifestyle phase, less than 50% succeeded in losing at least 5 kg, with patients who completed the programme being more successful. Participants who lost weight in the lifestyle phase were selected for FWL and experienced the greatest weight loss by the end of phase 2. Those who were unsuccessful in losing 5 kg through the lifestyle programme, were offered orlistat and LCD. The large sample size increased the precision of the results, while the stratification for potential confounding factors increased the study's validity. A higher proportion of patients were prescribed weight-neutral medications, compared with mixed and weight-gaining anti-diabetic medications. The proportion of patients on weight-gaining diabetes drugs referred to the GCWMS did not alter appreciably following the release of the SIGN guidelines. By the end of the lifestyle treatment phase, patients receiving weight-neutral drugs (metformin, DPP-IV, GLP-1, and SGLT2) were more successful in losing weight than those receiving weight-gaining drugs (SUs, TZDs, and any combination including insulin). The main recommendation from this research are, that further studies are carried out to better establish the best timing of use of orlistat within a weight management programme, that the intensity of phase 2 of the GCWMS is increased, and that prescribers take account of a patient's current BMI prior when prescribing anti-diabetic medication, especially when recommending weight loss and referring to a weight management programme.

Table of Contents

List of tables

List of figures

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Declaration

This thesis is submitted in fulfilment of the requirement for the degree of degree of Doctor of Philosophy at the University of Glasgow. I declare that the work in this thesis is original and has not been previously submitted for a higher degree to the University of Glasgow or any other institutions. One chapter of this thesis has been published with co-authors. The following publication and presentation originated from this thesis.

List of publications and presentations

Publications

Chapter 2

Aldekhail, N. M., Logue, J., Mcloone, P. & Morrison, D. S. (2015). Effect of orlistat on glycaemic control in overweight and obese patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials. *Obes Rev*, 16, 1071-80.

Presentations

The following abstract of this thesis was accepted for presentation at the following conference:

Aldekhail, N. M., Morrison, D. S., Logue, J. (2015). Evaluation of weight loss outcomes from the NHS Greater Glasgow and Clyde Weight Management Service (data from Chapter 3 and 4), paper presented to the 2nd UK Congress on Obesity (ASO), Glasgow, United Kingdom (September 9-11, 2015).

Abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AGB	Adjustable Gastric Banding
AHEAD	Action for Health in Diabetes
BMI	Body Mass Index
BNF	British National Formulary
BOCF	Baseline Observation Carried Forward
COPD	Chronic Obstructive Pulmonary Diseases
CHD	Coronary Heart Disease
CT	Computed Tomography
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DPP	Diabetes Prevention Programme
DPP-4	Dipeptidyl peptidase-4
DREAM	Diabetes Reduction Assessment with ramipril and rosiglitazone Medication
EASD	European Society for the Study of Diabetes
EOP	Exercise on Prescription
ES	Effect Size
F	Female
FDA	Food and Drug Administration
FTO	Fat mass and obesity associated gene
FPG	Fasting Plasma Glucose
FWL	Further Weight Loss
FWMS	Fakenham weight management service
GCWMS	Glasgow and Clyde Weight Management Services
GLP-1	Glucagon-like peptide-1
GP	General Practitioner
HbA1c	Glycosylated Haemoglobin
Hd	Hypocaloric diet
HMR	Health Management Resources
HTA	Health Technology Assessment

IARC	The International Agency for Research on Cancer
IFR	Individual Funding Request
IGT	Impaired Glucose Tolerance
ILI	Intensive lifestyle intervention
IWMC	Intensive Weight Management Clinic
LCD	Low Calorie Diet
LDL	Low-Density Lipoprotein
LED	Low-Energy Diet
LELDs	Low-Energy Liquid Diets
LOCF	Last Observation Carried Forward
M	Male
MRI	Magnetic Resonance Imaging
N	Number
NASH	Non-alcoholic Steatohepatitis
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NIHR	National Institute for Health Research
OECD	Organisation for Economic Co-operation and Development
Pa	Physical activity
PASI	Psoriasis Area and Severity Index
PDP	Personalised Dietary Prescription
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RCTs	Randomised Controlled Trials
Rf	Reduced fat
RYGB	Roux-en-Y Gastric Bypass
SAAT	Subcutaneous Abdominal Adipose Tissue
SBWI	Standard Behavioural Weight loss Intervention
SCI	Scottish Care Information
SG	Sleeve Gastrectomy
SGLT2	Sodium/glucose co-transporter 2
SIGN	Scottish Intercollegiate Guideline Network
SIMD	Scottish Index of Multiple Deprivation

SLiM	Special Lifestyle Management
SPICe	Scottish Parliament Information Centre
SQL	Structured Query Language
STEP	Stepped-care weight loss intervention
SU	Sulfonylureas
TNF	Tumour Necrosis Factor
TZDs	Thiazolidinediones
UK	United Kingdom
US	United States
VAT	Visceral Adipose Tissue
VCWM	Via Christi Weight Management programme
VLED	Very Low Energy Diet
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist-to-Hip Ratio
WMOR	Weight Management Programme On Referral
WOSCOPS	West of Scotland Coronary Prevention Study

Chapter 1: General introduction

Introduction

1.1 Epidemiology of obesity

1.1.1 Definition of obesity

Obesity has been defined by the World Health Organisation (WHO) (2000, 2013) as a medical condition in which the health of the individual is put at risk and/or the likelihood of mortality is enhanced due to the excessive increase in the body's fat storage capacity. To put it differently, obesity represents accumulation of fat beyond levels that are considered healthy. It is caused by the fact that the energy absorbed in the form of calories is greater than the energy consumed, with the unconsumed energy being deposited in different parts of the body as fat.

The risks to health depend on the manner in which the body fat is distributed. For example, as indicated by Jensen (2008), upper body or abdominal obesity is associated with greater health risks when compared to lower body or gluteal-femoral obesity, because in the former case the fat is mainly intra-abdominal or visceral, while in the latter case the fat is subcutaneous (Harvard Health Publications, 2006) and therefore is less dangerous to health as it accumulates under the skin rather than around the organs. Although a clear understanding of the heightened risks related to visceral fat is yet to be achieved, there is extensive evidence that visceral fat can contribute to metabolic disorders, cardiovascular disease and type 2 diabetes (Despres, 2012; Jensen, 2008). The Body Mass Index (BMI), which is determined based on an individual's weight and height, represents the standard tool of obesity measurement.

1.1.2 Incidence and prevalence

Using a BMI of 30 kg/m^2 and 25-29.9 kg/m^2 as the reference point to define 'obesity' and 'overweight', respectively, the WHO has estimated that, at global level, the number of individuals who are overweight has reached 1 billion; 300 million of who are classified as obese (WHO, 2014a). From 1995 to 2002, the total number of individuals with obesity rose by 100 million (Formiguera and Canton, 2004). By 2014, the number of individuals with overweight reached almost 1.9 billion with 600 million being classified as obese (WHO, 2014a). In percentages, this means that 39% of individuals older than 18 years of age are overweight and 13% are obese. Obesity is not restricted to certain countries or

areas but has become a global trend, with many countries, including China, having high numbers of individuals suffering from obesity. However, because obesity is the outcome of lifestyle and cultural choices as well as genetic factors, there are differences among countries in terms of how prevalent obesity is and how it occurs.

The countries with the highest obesity rate in 2011 were identified by the Organisation for Economic Cooperation and Development (OECD) as being the US (33.8%), Mexico (30%) and New Zealand (26.5%); while India (2.1%), Indonesia (2.4%) and China (2.9%) were listed as the countries with the lowest obesity rate in the same year (NHS Information Centre, Lifestyle Statistics, 2012). 25% each of male individuals of black Caribbean and Irish descent were found to be obese. Similarly, there were more female individuals of black Caribbean (32%), Pakistani (28%) and black African (38%) descent that were found to be obese than the percentage of people with obesity found in the general population, but fewer Chinese female individuals were found to be obese (8%) (NHS Information Centre, Health Survey, 2004). Initially, it was found in affluent countries that obesity was most prevalent and most likely to occur, but due to changing trends, obesity has now also become much more prevalent in moderately rich and poor countries. A direct correlation between a BMI $\geq$30 kg/m^2 and age was highlighted by the Scottish Health Survey (The Scottish Government, 2011). No significant difference relating to age was found in the proportions of male and female individuals having a BMI $\geq$30 kg/m^2 apart from individuals falling within the 16-24 year age group where it was found that 16.9% of the females and only 9.2% of the males had a BMI $\geq$30 kg/m^2.

1.1.3 Obesity in the male and female populations

Worldwide, the annual mortality rate among people who are overweight or obese is 2.8 million (WHO, 2014b). Obesity has become more prevalent throughout the world, having increased two-fold from 1980 to 2008. 35% of adult individuals were classified as overweight in 2008, with male and female individuals accounting for 34% and 35% of the whole population, respectively (WHO, 2014b). Furthermore, based on a BMI $\geq$30 kg/m^2, 10% of the global male population and 14% of the global female population were classified as being obese, which represents a two-fold increase compared to 1980, when there were fewer individuals with obesity on a global level (5% male and 8% female), although in affluent countries men's BMI exceeded that of women's. According to the Foresight Report, in the UK there are more male individuals who are overweight or obese than female individuals; 47% and 36% of male and female individuals are expected to

become obese by 2025 (Robertson *et al*., 2014). By contrast, in Scotland, more female individuals are obese than male individuals (29.3% vs. 24.9%) (The Scottish Parliament, 2015).

According to data reported by WHO (2014 b), the majority of overweight (62%) and obese (26%) adult individuals are in the Americas, whereas the fewest overweight (14%) and obese (3%) people are in Southeast Asia (Ogden *et al*., 2007). The WHO further indicated that over half of the female population of the Eastern Mediterranean, Europe and the Americas was overweight, while the female obesity proportions for these same regions were calculated to be 24%, 23% and 29%, respectively. Indeed, obesity levels were higher among female individuals than male individuals in every region covered by the WHO. Moreover, the obesity levels among females in Africa, the Eastern Mediterranean and Southeast Asia were almost double the levels among males **(Figure 1-1)**.

The WHO (2014b) has concluded that there is a greater predilection towards obesity among females than males. However, irrespective of gender, the likelihood of a BMI $\geq$30kg/m^2 is increased by factors such as lack of physical activity, living in a deprived area, not being fit for work, poor level of education, smoking, alcohol consumption, married status, having poor general health and suffering from a protracted illness. Social and economic factors (e.g. income level and occupation) have been found to increase the likelihood of obesity among females more than they did among males. A comparison between the two quintiles with the highest and lowest level of deprivation revealed that 33% of individuals in the former and 19% of individuals in the latter had a BMI $\geq$30 kg/m^2 (The Scottish Government, 2011). This could be because a person's economic status has an impact on their diet.

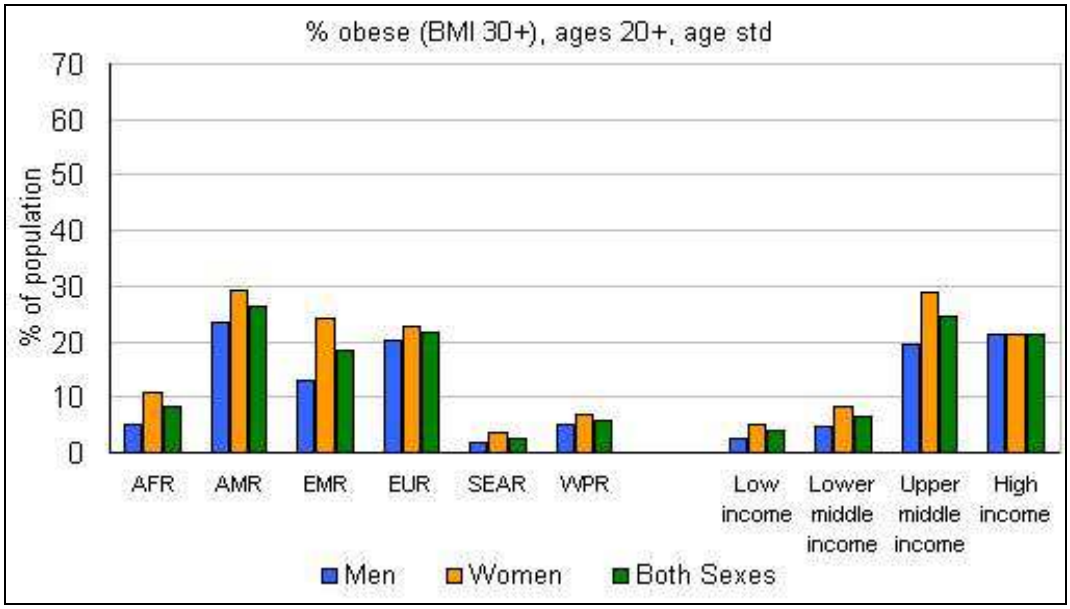

Figure 1-1 A graphical representation of the prevalence of obesity (WHO, 2014b) (AFR: Africa; AMR: Americas; SEAR: South-East Asia; EUR: Europe; EMR: Eastern Mediterranean; WPR = Western Pacific).

1.1.4 Obesity in the UK

There is increasing awareness in the UK about the serious health implications of obesity which, according to health authorities, is a major cause of mortality, but which is preventable. It has been estimated that by 2020 around 33% of the UK population could be obese (Seidell, 2006). The proportion of adults who are obese in the UK has reached 23.1%, which is greater than the average obesity rate of 15.5% in the rest of the European Union states (Freeman, 2010). Since 2009, about 25% of the adult population of the UK has been considered obese, with male and female individuals accounting for 22% and 24%, respectively. In 2010, 26% of the adult population of England was obese, with more men (42%) being overweight than women (32%) (NHS, Lifestyle Statistics, 2012). Furthermore, according to the Scottish Parliament Information Centre, the numbers of female adults who are overweight and obese are higher in Scotland than in England, Wales and Northern Ireland respectively (SPICe, 2015). On the other hand, the number of male adults with obesity is greater in both Northern Ireland and England than in Scotland.

1.1.5 Obesity in Scotland

Statistics regarding the rate of obesity in Scotland show a gradual rise in the number of individuals with obesity over the years. Since 1995, obesity levels have increased markedly among individuals in the 16-64 age range. An obesity rate of 17.2% in 1995 rose to 26.1% in 2012 and 27.1% in 2013, with 65% of adult individuals being considered overweight or

obese (The Scottish Government, 2014a). However, as observed by Keenan *et al*. (2011), this rate has not changed significantly since 2008. Over the same period, the proportion of individuals who are overweight or obese reached 61.9% in 2013, in contrast to 52.4% in 1995. Scotland is the fifth country in the world with the highest number of individuals with overweight or obesity and the sixth country with the highest rate of obesity. An overview of obesity trends and the numbers of overweight individuals in Scotland during the period from 1995 to 2013 is provided in **Figure 1-2** below (SPICe, 2015).

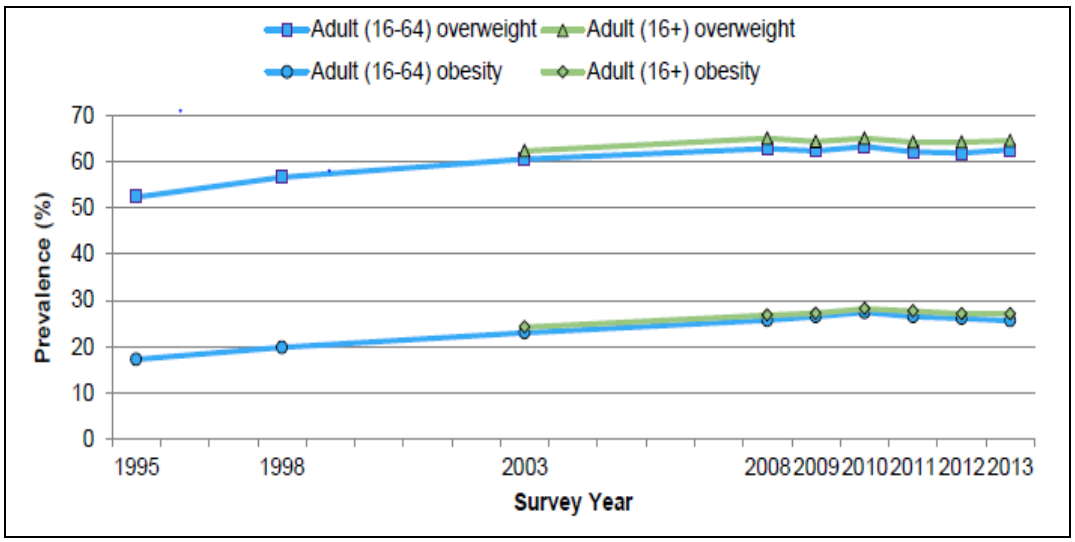

Figure 1-2 Number of Scottish adults with overweight and obesity (aged 16 to 64 years) from 1995 to 2010 and from 2003 to 2013 (aged ≥16 years). Source: SPICe. http://www.parliament.scot/ResearchBriefingsAndFactsheets/S4/SB_15-01_Obesity_in_Scotland.pdf.

1.2 Causes of obesity

1.2.1 Genetic history

As high calorie foods have become increasingly available and the opportunities for physical activity have decreased, a growing number of people at global level have become obese in recent years (Formiguera and Canto´n, 2004). This trend is to some extent rooted in genetic factors, despite the fact that the extremely slow occurrence of variation in populations' genetic composition means that such factors are not wholly accountable for the increasing obesity rate (Walley *et al*., 2009). There is some consensus among scientists that genes play a role in the regulation of food-derived energy assimilation, storage and consumption by the human body. Out of the various genes considered to make an individual prone to becoming obese (O'Rahilly and Farooqi, 2006), the major one is the fat mass and obesity-associated gene (FTO), which has been the focus of extensive research since its identification in 2007 (Frayling *et al*., 2007). Shinozaki and Okuda (2012) reported that, within the general population, FTO variations have been associated with a 0.39 kg/m^2 body mass increase, while variations in the areas proximal to MCR4 genes have been related to an increase in body mass of 0.23 kg/m^2 to 0.25 kg/m^2 (Zobel *et al*., 2009). Furthermore, according to Herrera *et al*. (2011), genetics can help shed light on 40-70% of variability in proneness to obesity.

Environmental and genetic factors must be afforded equal importance in any investigation of the increase in the rate of obesity throughout the world. From a genetic perspective, a frequently invoked explanation is the development of an imbalance between the environment and the internal structure of the body. Fawcett and Barroso (2010) have suggested that significant environmental transformations have led to modifications in the functions of the so-called thrifty genes, which enabled early people to withstand periods of food shortages.

Different studies have supplied scientific proof suggesting an indirect correlation between obesity and genetics (Gregg *et al*., 2003). Such proof is usually the outcome of research into similarities and discrepancies between family members, adopted individuals and twins. Research has also focused on certain genes that are found more extensively in people with obesity. Although this kind of research identifies genetic factors as the most likely cause of many of the weight variations observed in adult individuals, the exact nature of such factors is not yet known (McCarthy, 2010; Barry *et al*., 2009). Genes have been identified as being the direct determinants of an individual's weight in research

conducted on identical twins (Silventoine *et al*., 2010). Thus, an individual who is overweight or obese is likely to be so due to genes inherited from parents who are overweight or obese. In addition, the body's capacity for fat storage and the distribution of fat are significantly influenced by genes. Furthermore, since physical activities and dietary patterns are shared within families, genes are closely correlated with the environment.

1.2.2 Lifestyle factors

1.2.2.1 Diet and eating habits

Lifestyle choices and dietary patterns are generally considered to be the major reasons why individuals become overweight or obese. Throughout the world, obesity is mostly due to excessive eating and the eating of unhealthy food, such as processed food or food with a high fat content (Perez-Cueto *et al*., 2010) as opposed to vegetables, fruit and unrefined carbohydrates. Alcoholic drinks and soft drinks containing large quantities of sugar also cause an increase in body weight (Powers and Bruty, 2009; Ludwig *et al*., 2001) and therefore their consumption should be avoided (Ebbeling *et al*., 2006).

McNeill and Cummings (2004) suggest decreasing the amount of calories consumed per day by 600 calories, that is, 20-25% of the energy intake, to achieve what is considered to be an appropriate weight loss of 0.5 kg weekly. Ordering a starter and dessert in addition to the main course in a restaurant is considered excessive eating which can lead to obesity, especially if the amount of fat in the consumed foods is high. Bes-Rastrollo *et al*. (2013) systematically reviewed studies on the correlation between weight increase and drinks with high sugar levels and found that ten out of twelve (83.3%) reviews with no specified conflict of interest confirmed that weight increase was indeed related to consumption of sugary drinks. Furthermore, the family plays an important role in an individual's development of unhealthy dietary patterns.

1.2.2.2. Physical activity

Any movement of the body determined by the activation of skeletal muscles and leading to energy consumption can be considered to be physical activity (Caspersen *et al*., 1985). The implications of both physical activity and of the lack of physical activity have come into sharper focus due to research conducted in the last ten years. A direct correlation has been established between the lack of physical activity (i.e. sedentariness) and heightened risks of

chronic health conditions such as obesity, diabetes and cardiovascular disease (Van der ploeg *et al*., 2012). The reason for this is that energy intake is greater than energy release. The physical activity levels of the majority of adult individuals are insufficient to ensure fitness and prevent obesity, contributing to the elevated rate of obesity at a global level. According to Wright and Aronne (2012), the lack of physical activity is due to the fact that technological innovations have diminished the necessity for people to engage in physical tasks.

1.2.2.3. Other factors

Ex-smokers are likely to gain weight both because the smell and taste of food improves when one stops smoking (Sahlin *et al*., 2009) and also because the body metabolism does not function as fast as it does when there is nicotine in the system, resulting in reduced energy consumption (Chiolero *et al*., 2008). Although the majority of studies have argued that smoking and adipose levels are negatively correlated, the manner in which fat is distributed in smokers is more harmful to the metabolism and the rise in BMI is directly proportional to smoking frequency (Kim *et al*., 2012). In comparison to individuals who do not smoke and have a normal BMI, those who do smoke and have a high BMI are 6 to 8 times more likely to die from obesity-related conditions. Furthermore, in comparison with individuals who do not smoke and have a normal waist circumference (WC), smokers who have a high WC are more than five times more likely to die than non-smokers with a normal WC.

The increasing rate of obesity throughout the world is also tied to the fact that people are living longer. Loss of muscle mass is a common consequence of age advancement, particularly in the case of sedentary individuals. This in turn reduces energy consumption, which increases the probability of weight gain, especially if the energy intake is higher (Sahlin *et al*., 2009). As indicated by the findings of cross-sectional studies, the rise in obesity levels is directly proportional to age increase, accelerating between the ages of 20 and 30 and continuing until the late 50s (Rolland-Cachera *et al*., 1991). Meanwhile, an important determinant of obesity prevalence is income, which reflects socioeconomic standing. In England, the BMI of female individuals with a lower income is higher than that of female individuals with a higher income (average BMI 27.7 kg/m^2 vs. 26.5 kg/m^2), but no correlation has so far been established between income and BMI in the case of male individuals (NHS, 2013). By contrast, a general association has been established between lower socioeconomic standing and higher obesity rates in Scotland (SPICe, 2015).

The caloric content of alcohol is considerable and therefore drinking alcohol directly leads to weight gain. In addition, it has been demonstrated that weight gain is also triggered by alcohol consumption indirectly because it enhances appetite and the sensation of being hungry in the short-term (Sahlin *et al*., 2009). Pregnant women are more predisposed to weight gain, due to the fact that foetus' development demands higher amounts of energy and nutrients. However, many women struggle to return to their normal weight after they give birth (Sahlin *et al*., 2009), thus increasing the likelihood of becoming overweight or obese, particularly if they have been through more than one pregnancy (multiparity).

Another factor that can heighten the likelihood of obesity is lack of sleep. During sleep, the hormones ghrelin and leptin, which are respectively linked to the sensation of hunger and satiety, are regulated by the body. However, the ghrelin levels increase and the leptin levels decrease when an individual has not slept sufficiently (Sahlin *et al*., 2009), making them feel hungry. Furthermore, Wright and Aronne (2012) have suggested that a negative correlation exists between the number of hours slept per night and BMI, with fewer hours of sleep stimulating cravings for carbohydrate- and calorie-rich foods and excessive eating, resulting in weight gain.

1.2.3. Use of medication

Evidence exists that a range of prescription medication intended for health and wellbeing causes body fat levels to rise, thus leading to weight gain. It is still unclear how prescription medication determines weight gain exactly, but it has been demonstrated that some medication, such as medication for diabetes, depression, inflammation, and convulsion, is accompanied by side-effects such as an increased sense of hunger or water retention (Malone, 2005), as well as a reduction of the metabolic rate, leading to increased sedentariness. **Table 1-1** lists a number of agents that may cause weight gain or are weight neutral. The sensation of hunger is enhanced by some medication which acts on the brain and triggers modifications in the centre concerned with satiety. There are a number of considerable dangers related to weight gain and higher BMI caused by prescription medication, including an increased level of cholesterol, hypertension, and risk of diabetes. Some medication may induce weight gain in a short period of time, resulting in adverse cardiac effects and leading to hypertension, which requires immediate medical attention.

Prescription medication alternatives may be suggested in certain cases, although these may also have secondary effects and may therefore not provide a viable solution. Furthermore, as noted by Seagle *et al*. (2009), not all people respond in the same way to particular medications, so the effects may vary. For example, a certain type of medication may cause some individuals to lose weight and have no effect on others.

Drug groups	**Example of weight gain drugs**	**Example of weight neutral/loss drugs**
Anti-diabetic agents	Insulin, SUs and TZDs.	GLP-1, metformin, SGLT2
Psychiatric agents	Fluoxetine, citalopram amitriptyline, olanzapine, risperidone	Bupropion, Tranylcypromine
β-adrenergic blockers	Propranolol, atenolol	-
Neurologic agents	Valproic acid, carbamazepine	Lamotrigine, topiramate

Table 1-1 List of medications that may cause weight gain or are weight neutral.

1.3 Body composition measurement

Epidemiological studies have highlighted the fact that to determine how the reflective body adipose tissues are distributed, there is no need for complicated densitometry or imaging methods, as anthropometric measurements (i.e. body dimensions and weight measurements) are sufficient. These measurements provide an indication of an individual's predisposition towards obesity based on the determination of adipose tissue levels. The statistical correlations between the weight and size of the body have enabled the formulation of accurate limits for overall body fat volume (Heim *et al*., 2010).

In the UK, threshold values associated with morbidity and mortality, especially in the case of non-transmittable conditions such as type 2 diabetes and cardiovascular disease (CVD), have been established (National Obesity Observatory, 2009). Apart from BMI, there are two additional fundamental anthropometric measurements for adults, namely, WC and waist to hip ratio (WHR).

1.3.1 Body Mass Index (BMI)

Calculated as the body weight divided by the square of the body height (kg/m^2), the BMI indicates the overall body fat volume, but does not reflect how the fat is distributed. Its measurement is straightforward and accurate and most individuals have no trouble understanding it (WHO, 2013). A BMI that exceeds 25 kg/m^2 is considered to be a clear indicator of all-cause mortality (Calle *et al*., 1999). However, the fact that it cannot differentiate fat mass from lean mass is a major drawback of the BMI, because it can lead to errors of categorisation of younger and older people. On the other hand, evidence gathered by previous studies suggests that patients who are overweight have a lower risk of suffering from cardiovascular disease and have better survival rates than those with a BMI within the normal range (Romero-Corral *et al*., 2006; Oreopoulos *et al*., 2008).

Pischon *et al*. (2008) argued that, in the case of young adults, obesity is overestimated by the BMI measure. Young individuals can be classified as overweight even though what causes high BMI values may be lean mass rather than fat mass, which means that their risk of morbidity is reduced because they are fitter (Pischon *et al*., 2008). On the other hand, obesity may be underestimated by the BMI measure in the case of individuals who are older or who are not of white ethnicity, due to the fact that the level of body fat of these individuals is greater than that of younger individuals. Additionally, the degenerative

processes that accompany age advancement cause a reduction in the height of older individuals.

The National Institute of Clinical Excellence (NICE) (National Obesity Observatory, 2009) states that optimum cut-off values have not yet been clearly defined in the case of older individuals. In the case of individuals of Asian origin, the issue is further complicated because they seem to be more at risk of health conditions associated with obesity even if they have a normal BMI (Pischon *et al*., 2008). Therefore, the intermediate cut-off values of 23 kg/m^2 ("increased risk") and 27.5 kg/m^2 ("higher risk") have been introduced for this population (WHO Expert Consultation, 2004). Compared to individuals with overweight or those of normal weight, individuals who are obese are more likely to develop diseases. Nevertheless, as stressed by Mei *et al*. (2002), BMI cannot be used to diagnose obesity but only to screen for obesity. The classification of body weight and the risk of health complications can be seen in **Table 1-2**.

BMI (kg/m^2)	Definition	Associated health risks
Underweight	<18.5	Low (but increased the risk of other clinical problems)
Normal-weight	18.5 to 24.9	Average
Overweight	25 to 29.9	Increased
Obese	≥30	
Class I	30 to 34.9	Moderately increased
Class II	35 to 39.9	Severely increased
Class III	≥40	Very severely increased

Table 1-2 Different cut off points and classifications of obesity into various groups.

1.3.2 Waist Circumference (WC)

WC is a surrogate measure for visceral fat and provides a cheap, accessible, simple measure. Abdominal adipose tissue can be measured by computed tomography (CT) and magnetic resonance imaging (MRI), and these techniques are able to differentiate between subcutaneous abdominal adipose tissue (SAAT) and visceral adipose tissue (VAT). The advantage of the two techniques is that they provide accurate results; however, the services they provide are expensive so their use is limited to hospitals and research centres. The processes also take a long time and therefore these techniques are unsuitable for use in large sample studies (Browning *et al*., 2011). According to Pischon *et al*. (2008), WC must

be better defined to enable distinctions to be made between different stages of obesity that would help health professionals to predict the risks related to high WC with greater precision. The presence of high levels of adipose tissues in the abdominal cavity and surrounding the organs is indicated by a high WC value; compared to subcutaneous fat, this kind of visceral fat poses greater health risks. Numerous community and clinical organisations at both the local and the international level have adopted the sex-related intervention thresholds proposed by the WHO **(Table 1-3)**.

Classification	Men	Women
Normal-weight	<94 cm	<80 cm
Overweight	94 cm to 102 cm	80-88 cm
Obese	>102 cm	>88 cm

Table 1-3 Waist circumference categories.

WC can estimate abdominal fat and overall fat levels in an effective and straightforward way that is not connected to height. Owing to its efficiency in determining overall fat levels, WC has been used instead of BMI in clinical practice. On the downside, obtaining WC data is not as easy as obtaining BMI data because of several reasons, including the need to use a measuring tape, discomfort felt by individuals at having to take off their clothes, as well as the requirement to measure a particular area of the body. Stevens *et al*. (2010) conducted a prospective study involving up to 300,000 European participants and revealed that WC could anticipate the likelihood of death from obesity-related complications separately from BMI. Similarly, a review of cross-sectional and prospective studies by the WHO indicated a close correlation between WC and CVD as well as between WC and type 2 diabetes. Pischon *et al*. (2008) also reported that high fat levels in the abdominal cavity measured with WC instead of BMI were closely correlated with metabolic syndrome, diabetes, CVD, and all-cause mortality.

1.3.3 Waist-to-hip ratio (WHR)

Measured in centimetres, the WHR indicates how the waist circumference is related to the hip circumference. Based on risks and the likelihood of mortality, the WHO has established sex-particular thresholds for WHR as it did for WC **(Table 1-4)**.

Classification	Men	Women
Normal-weight	<0.94	<0.80
Overweight	0.94 to 0.99	0.80-0.84
Obese	≥1	≥0.85

Table 1-4 Waist-to-hip-ratio categories.

Although WHR can be used instead of WC to measure abdominal adiposity, the higher risks associated with high WHR values may stem from either abdominal fat or from a smaller body stature and frame, making interpretation of this index more challenging (Pischon *et al.*, 2008). The hip circumference is indicative of both body fat and body stature and frame. Meanwhile, the prospective study carried out by Janssen *et al.* (2004) has revealed that, in the case of older individuals, mortality can be more effectively anticipated by WHR than by BMI, especially death as a result of myocardial infarction and CVD. On the other hand, there is evidence that individuals with a small hip circumference are more prone to diabetes and cardiovascular complications (Heim *et al*., 2010).

An earlier review found that the cut-offs for threshold of higher risk WHR in South Asian ethnic groups was ≥0.80 and ≥0.90 for women and men respectively (Lear *et al*., 2010). Lower cut-off thresholds for non-European groups have also been proposed by numerous studies. However, the predictability of WHR is not as good as that of WC because of issues related to the collection of data through measurement. To ensure the validity and reliability of the data, two measurements must be taken and the person taking the measurements has to touch the individuals being measured on the waist and the hips (Heim *et al*., 2010), creating a potentially uncomfortable situation for the persons being measured.

Valid association between WHR measurements and certain conditions such as CVD, type 2 diabetes, high blood pressure, and specific types of cancers, particularly breast cancer (Heim *et al*., 2010). Factors such as age, sex and ethnicity do not influence the accuracy of WHR in indicating abdominal adiposity. Furthermore, BMI, WC and WHR may differ in terms of their interpretation as indicators of CVD and type 2 diabetes, but the differences are not marked and lack statistical significance. Janssen *et al.* (2004) reviewed data from across the UK but did not find evidence that BMI, WHR and WC estimates differed significantly. Nonetheless, out of the three indices, WHR is considered to estimate high cholesterol levels most accurately. There is substantial evidence in favour of high odd

ratios once other obesity indicators are taken into account, but even after BMI and WC adjustment, WHR is still associated with the highest degree of prediction.

1.4 Obesity-related morbidity and mortality

Health is adversely affected by obesity in a variety of ways. People with obesity are more likely to suffer not only from CVD, high blood pressure and peripheral vascular disease, but also from changes in lung function, such as reduced lung compliance, anomalies of ventilation and perfusion, and respiratory muscle weakness and diminished performance. Depressed ventilator drive, obstructive sleep and bronchospasm are also likely consequences of obesity. Sternal wound infections and leg infections may also develop in individuals with obesity (Gronniger, 2006). In the US alone, around 300,000 people die from obesity-related complications every year. Sleep apnoea, respiratory problems, high blood pressure, joint degeneration (e.g. osteoarthritis) and cancer, especially in female individuals, are the most pervasive implications of obesity.

1.4.1 Cardiovascular diseases

Most individuals with hypertension are typically overweight and are six times more likely to experience hypertension-related complications than individuals of normal weight (Alwan, 2011). Furthermore, as emphasised by Poirier *et al*. (2006), in addition to being more prevalent among individuals who are overweight, high blood pressure can also develop in young individuals who gain weight. For instance, an increase in body weight of 10 kg elevates the systolic and diastolic blood pressure by 3 mmHg and 2.3 mmHg, respectively, which in turn heightens the likelihood of chronic heart failure and stroke by 12% and 24%, respectively. Brown *et al*. (2000) reported that the prevalence of hypertension in men increased progressively with the BMI increasing from 15% at a BMI of $\leq$25 kg/m^2 to 42% at a BMI of $\geq$30 kg/m^2.

The blood volume, stroke capacity and cardiac output are all elevated in individuals who are overweight. In individuals whose blood pressure is normal, such a high output state is associated with diminished peripheral vascular resistance (Trullas *et al*., 2013), but in individuals who are obese this resistance is inadequate or elevated in the presence of hypertension (Lavie *et al*., 2009). There are two main causes underpinning the factors associated with hypertension and ensuing coronary heart disease:

1. The effect of obesity on body hemodynamics
2. Processes such as defective endothelial function, resistance to insulin, anomalies in the sympathetic nervous system, and adipocyte-produced cytotoxic substances that create a direct correlation between obesity and elevated peripheral resistance.

Another perspective that is gathering support is that obesity plays a role in the activation of the sympathetic nervous system and alterations in renal morphology and function. Evidence also exists that hypertension in the people with obesity develops with the crucial involvement of renal dysfunction manifested as enhanced tubular sodium reabsorption and the resetting of pressure natriuresis. In addition, Krauss *et al*. (1998) indicated that obesity is correlated with dyslipidaemia, while increased LDL-C, low HDL-C and proliferation of triglycerides are all caused by excessive weight.

In the case of female individuals, the correlation between obesity and hypertension is not very different, with BMI of 25 kg/m^2 and 30 kg/m^2 being respectively associated with 15% and 38% likelihood of coronary artery disease as a result of the fact that arteriosclerosis develops in the main arteries that supply the myocardium (Lavie *et al*., 2009). Aside from interfering with body hemodynamics, obesity also enhances the demand for oxygen to about 15 ml/kg per minute, causing the heart to work harder (Gluckman *et al*., 2009) and resulting in a rise in the blood volume. Shihab *et al*. (2012) indicated that the likelihood of incident hypertension was greater among male individuals in the US who are overweight or obese than among male individuals of normal weight.

Earlier studies suggested that obesity is an independent risk factor for coronary heart disease (CHD) and atherosclerosis (Lavie *et al*., 2007; 2009). The relationship between BMI and the risk of CHD events is poorly understood, due to the effect of other potential confounding factors such as non-intentional weight loss, smoking and medication. In the West of Scotland Coronary Prevention Study (WOSCOPS) that comprised 6,082 male participants, Logue *et al*. (2011) found that obesity was associated with an increased risk of fatal CHD events after an adjustment was made for confounding factors. A collaborative analysis of large prospective studies (comprising 894,576 participants), undertaken by Whitlock *et al*. (2009), found a 30% increase in mortality for every 5 kg/m^2 increase in BMI above 25 kg/m^2. Mortality was higher in those with a BMI of 30-35 kg/m^2 (median survival was reduced by 2-4 years) and a BMI of 40-45 kg/m^2 (reduced by 8-10 years). It has been suggested that the excess mortality was due to vascular disease; whereas, the higher mortality of people with a BMI below 22.5 kg/m^2 was due to smoking related diseases or malnutrition. Additionally, in the 14-year follow-up of the Framingham Heart Study participants (Kenchaiah *et al*., 2002), it was found that the risk of heart failure increased 5% and 7% in men and women respectively for every 1 kg/m^2 increase in BMI.

1.4.2 Type 2 diabetes

Type 2 diabetes has become markedly more prevalent in the last two decades. In Scotland, around 284,122 people were diagnosed with diabetes and this represents 5.3% of the population (NHS Scotland, 2015). Regardless of the fact that type 2 diabetes is more prevalent in patients with obesity, 13% of individuals with type 2 diabetes had a BMI of 18.5-24.9 kg/m^2, 31.5% had a BMI of 25-29.9 kg/m^2, and 55.5% had a BMI ≥30 kg/m^2 (NHS Scotland, 2014). There is ample research that supports the fact that weight gain and obesity enhance the likelihood of type 2 diabetes, especially among individuals with higher levels of abdominal fat as opposed to fat in the peripheries of gluteal-femoral areas of the body (Kissebah and Krakower, 1994).

According to Hu *et al.* (1999), female individuals are more likely to have type 2 diabetes if they are obese and do not engage in physical activity. Similarly, Carey *et al.* (1997) indicated that a BMI ≥23 kg/m^2 heightens the risk of diabetes, while a BMI ≥35 kg/m^2 is associated with almost 100 relative risks. Eckel *et al.* (2011) investigated the correlation between type 2 diabetes and obesity and discovered that the development of type 2 diabetes has an adverse impact on the function of pro-inflammatory cytokines such as Tumour Necrosis Factor (TNF) and Interleukin-6 (IL-6), mitochondria, insulin resistance, fatty acid metabolism, and the endoplasmic reticulum. People with obesity have higher levels of free fatty acids, which determine a decrease in insulin production and an overproduction of hepatic glucose (Boden, 2008). In fact, the elevated prevalence of type 2 diabetes is based on obesity and the distribution of visceral fat as a major risk factor. As explained by Mancini and Halpern (2008), a chronic inflammatory condition with resistance to insulin may develop as a result of the substances contained in visceral fat.

Formiguera and Canton (2004) argued that obesity and type 2 diabetes are primarily linked through insulin resistance, which refers to the fact that insulin can no longer regulate the metabolism of carbohydrates and lipids effectively. In individuals with obesity and type 2 diabetes, insulin resistance takes the form of reduced transport and metabolism of glucose in adipocytes and skeletal muscle as well as dysfunctional inhibition of hepatic glucose output (Formiguera and Canton, 2004). When the pancreas is no longer able to overcome insulin resistance by producing sufficient insulin, it leads to the development of type 2 diabetes.

Furthermore, Ye (2013) reports that glucose homeostasis is affected in different ways by the various adipose tissue sub-types, as these do not have the same function. Among the different processes underpinning the correlation between obesity and type 2 diabetes are cytokine overproduction, deposition of ectopic adipose tissue, and inadequate functioning of the mitochondria. A moderate decrease in body weight is enough to avoid both type 2 diabetes and obesity; this can be achieved in various ways, including lifestyle changes, behavioural intervention, obesity drugs, or bariatric surgery (SIGN 116, 2010).

1.4.3 Cancer

According to statistics reported by Vucenik *et al.* (2012), in the UK, one out of twenty types of cancers is associated with obesity or higher-than-normal weight. Research has revealed that individuals with overweight are more likely to develop certain types of cancer. As stated by the International Agency for Research on Cancer (IARC), the existing evidence is ample enough to support the correlation between obesity and cancer, especially, post-menopausal breast cancer, oesophageal adenocarcinoma, endometrial cancer, colorectal cancer and renal cell cancer (IARC, 2002). Fat deposition and exposure to growth factors are the reasons that increase the susceptibility of individuals with overweight to the influence of hormones. Furthermore, individuals who are obese are more likely to develop some types of cancers because the oestrogens in their blood are higher than usual.

To determine how a BMI rise of 5 kg/m^2 is correlated with the risk of twenty types of cancers with greater or lesser prevalence, Renehan *et al.* (2008) carried out a meta-analysis and found that the risk of endometrial cancer (RR 1.59, 95% CI: 1.5 to 1.68, p <0.001), oesophageal adenocarcinoma (RR 1.59, 95% CI: 1.31 to 1.74, p <0.001), kidney cancer (RR 1.34, 95% CI: 1.25 to 1.43, p <0.001) and gallbladder cancer (RR 1.59, 95% CI: 1.02 to 2.47, p =0.04) was considerably higher, especially in female individuals. Furthermore, the increase in BMI was also significantly correlated with leukaemia, postmenopausal breast cancer, thyroid cancer, multiple myeloma, pancreatic cancer and colon cancer. On the other hand, male individuals were particularly at risk of oesophageal adenocarcinoma, colon cancer, thyroid cancer and renal cancer, as well multiple myeloma, rectal cancer, malignant melanoma and leukaemia.

1.4.4 Respiratory diseases

Obesity may also trigger different respiratory problems. Elevated ventilation demand, tissue perfusion, breathing overload, reduced functional residual capacity, low performance of respiratory muscles, and peripheral lung segment blockage are common occurrences in people who are overweight. As explained by Zammit *et al.* (2010) such conditions usually result from the fact that the ventilation demand is not balanced with perfusion insufficiency, particularly in a prone position. Severely people with obesity often develop obstructed respiratory syndrome.

Severely individuals who are obese display respiratory insufficiency and pulmonary hypertension. As the expanding pulmonary structures are subjected to increased pressure due to the greater weight, sleep disorders and breathing obstructions are highly prevalent among individuals with obesity. The condition known as sleep apnoea is characterised by recurring intervals of breathing obstruction and hypopnoea during sleep, a sensation of sleepiness during the day as well as irregular cardiopulmonary function (Zammit *et al.*, 2010). Furthermore, Murugan and Sharma (2008) highlighted the fact that additional respiratory diseases are also more likely to develop in people who are obese, such as bronchial asthma, pneumonia, pulmonary embolism, pulmonary hypertension, deep vein thrombosis and chronic obstructive pulmonary disease.

1.4.5 Additional obesity-related morbidities

The hormonal irregularities that accompany obesity are responsible for about 6% of primary infertility, interfering with normal reproductive function in the case of women and making men impotent (Esposito *et al.*, 2004). Furthermore, the kidneys, liver, gall bladder, muscles and bones, and the endocrine system are all severely affected by the increased levels of lipids in the body (Reeuwijk *et al.*, 2010). The likelihood of secondary disorder development increases in direct proportion with the levels of adipose tissue in the body.

The kidneys are under massive pressure in individuals who are obese as they have to eliminate the toxins and sustain the demands made by an elevated BMI on the metabolism. As a result of hyperfiltration, the likelihood of kidney disease is high. Additional condition that is prevalent in individuals with obesity is osteoarthritis (OA), and additional musculoskeletal conditions such as back pain and gout (Grotle *et al.*, 2008). Moreover, compared to individuals of normal weight, people with obesity are more likely to develop

cholelithiasis and cholecystitis, while their risk of developing Alzheimer's disease is 42% greater (Beydoun *et al.*, 2008).

1.5 Health implications of weight reduction

The findings of the review of weight loss studies conducted by Poobalan *et al.* (2007) revealed that conditions associated with obesity, such as diabetes, high blood pressure, and high cholesterol and LDL levels, all improved as a result of a weight reduction of 5-10%. According to the Action for Health in Diabetes (Look AHEAD) study, substantial weight reduction also leads to ample clinical benefits (Wing *et al*., 2011). However, it remains unknown whether clinical outcomes such as myocardial infarction, stroke and sudden death are influenced in any way by weight reduction.

1.5.1 Weight loss and mortality

The link between obesity and increased risk of mortality is well documented. However, studies found that patients suffering from obesity and other diseases such as rheumatoid arthritis or heart failure were associated with decreased mortality "obesity paradox". For example, in a meta-analysis of studies with a total of 28,209 participants with cardiac failure (Oreopoulos *et al*., 2008), patients with a BMI of 25-29.9 kg/m^2 and BMI $\geq$30 kg/m^2 had 16% and 27%, lower all-cause mortality respectively than patients with a BMI of 18.5-24.9 kg/m^2 during a period of 2.7 years. In a prospective cohort of 779 participants with rheumatoid arthritis, Escalante *et al*. (2005) found that, after adjusting for smoking, medication and duration of disease, the mortality rate was 66% lower in patients with a BMI >30 kg/m^2 than those with a BMI of 20-24.9 kg/m^2.

The results of the study conducted by Gregg *et al.* (2003) indicated that the likelihood of death decreased when moderate deliberate weight reduction was achieved, but the likelihood of death increased as a result of inadvertent weight reduction in the case of overweight and obese adult Americans aged 35 years or older. Likewise, Wannamethee *et al.* (2000) reported that the mortality rate rose by 29-77% due to inadvertent weight reduction, owing to the natural history of a range of conditions, including depression, end-stage heart disease, and cancer. Likewise, the mortality rate decreased by 25% among female and male individuals with diabetes-related weight reduction, while a weight reduction of 20-29lb (9-13 kg) led to the most significant mortality rate decrease of 33% (Williamson *et al.*, 2000). Moreover, a prospective cohort study (Sjostrom *et al*., 2007) of 2,010 participants who had bariatric surgery and 2,017 who were following conventional treatment programmes, showed that over 10.9 years of follow up, the overall mortality rate within the surgery group was reduced by 29% (101 deaths in the surgery group and 129

deaths in the control group). Another retrospective cohort study carried out by Adams *et al*. (2007), involving 9,949 patients who had undergone gastric bypass and a control group of participants suffering from severe obesity who applied for driver's license, found that, over 7 years, long-term mortality decreased by 40% among the surgery group and there were 92% fewer deaths caused by diabetes and 60% fewer deaths caused by cancer.

On the other hand, Trullas *et al.* (2013) reported that no BMI category was associated with a heightened mortality risk as a result of weight reduction equal to or greater than 5%. However, there are some chronic debilitating conditions, such as cardiac cachexia or chronic obstructive pulmonary disease (COPD), that lead to massive weight reduction, which increases the likelihood of death (Graessler *et al.*, 2009). Furthermore, some studies have suggested that all-cause mortality benefits differ according to sex. Indeed, Poobalan *et al.* (2007) revealed that female individuals who deliberately lose weight enjoy all-cause mortality benefits in the long-term, but the long-term benefits for male individuals are yet to be fully elucidated.

In conclusion, in the general population, the risk of mortality increases with a BMI >25 kg/m^2; however, a higher BMI in people with a disease such as CHD or rheumatoid arthritis is associated with a decrease in the mortality rate. A study by Martin-Ponce *et al*. (2010) that included 400 patients aged ≥60 years who were hospitalised at the internal medicine unit found that patients who suffered from obesity had a better long-term survival chance than those with lower BMI scores. The study also concluded that people with obesity were younger, suffered less from anorexia, had better nutrition and had more muscle mass. It has been suggested that the better odds of survival associated with obesity are due to factors other than any beneficial effects of excess weight, such as reverse causality due to disease-related weight loss. Additionally, it is suggested that in case of ageing and illness with obesity, a "healthy BMI may be >25 kg/m^2, but not over 30 kg/m^2.

1.5.2 Diabetes

Complicated comorbidities are more likely to occur in individuals with obesity and type 2 diabetes (Nilsson, 2008). According to the findings of a number of studies, lifestyle modifications, including physical activity, medication, and surgery, are effective in helping diminish the incidence of type 2 diabetes in relation to obesity (Nilsson, 2008). However, it is still unclear how weight loss benefits patients with type 2 diabetes. Souto-Gallardo Mde *et al.* (2011) have reported that hypoglycaemic medication was needed less frequently

and/or diabetes showed remission as a result of weight reduction. Similarly, Aucott *et al.* (2004) revealed that the status of type 2 diabetes and impaired glucose tolerance (IGT) improved after moderate weight reduction.

The Look AHEAD study reported a correlation between weight reduction and enhanced diabetes control. Carried out in the US, this study comprised 5,145 overweight and obese individuals with type 2 diabetes who were randomly divided into two groups; where members of one group receiving standard diabetes support and education and members of the other receiving intensive lifestyle intervention. The latter programme consisted of collective and one-on-one meetings geared towards reducing weight and hindering renewed weight gain via an approach involving lower energy intake and enhanced physical activity (Pi-Sunyer *et al.*, 2007). At baseline, all participants had a BMI $\geq$25 kg/m^2 or $\geq$27 kg/m^2 in the case of those taking insulin. Additionally, all participants were older than 40 years of age. The main goal was to establish whether an approach combining diet, physical exercise and behavioural changes, including formulation of objectives and maintenance of weight reduction to 7% or more of the original body weight, could accomplish long-term weight loss that would lower cardiovascular morbidity and mortality in patients with type 2 diabetes. Male and female participants with type 2 diabetes were subjected to an exercise test, since the ultimate goal was to diminish the risk of cardiovascular conditions, while weight loss was a primary objective.

Participants were not included for randomisation in the intervention group if they did not satisfy the criteria for age-related maximal heart rate. Registered dieticians, behavioural psychologists, exercise specialists and lifestyle counsellors made up the intervention teams that managed the sessions. They met with the participants regularly during the first six months, with an individual session being scheduled during the fourth week of each month. The results revealed that the intervention group accomplished 8.6% weight loss (P <0.001) when the support group achieved only 0.7% weight loss. At twelve months, people with type 2 diabetes lost a significant amount of weight owing to the intensive intervention, resulting in better diabetes management and diminished risk of CVD and use of drugs (Pi-Sunyer *et al.*, 2007).

Williamson *et al.* (2000) conducted a prospective study on 4,970 participants with type 2 diabetes who were 13 years or older, who were monitored for deliberate and inadvertent weight reduction. Results showed that mortality due to cardiovascular disease and diabetes decreased by 28% among those who lost weight deliberately. In a different study, the

medical records of deceased individuals with type 2 diabetes were investigated by Lean *et al.* (1990), who observed that individuals lived 3-4 months longer for every kilogramme of weight lost. Similarly, Knowler *et al.* (2002) reported that the risk of type 2 diabetes was considerably lowered by modest weight reduction of 3-4 kg (5%).

The Diabetes Prevention Programme (DPP) showed that it was possible to prevent the onset of type 2 diabetes with an intensive programme of lifestyle changes and diet. The DPP succeeded in reducing the incidence of type 2 diabetes by 58% in a population that was at high risk of developing this disease by lifestyle intervention and physical activity that aimed to achieve 7% weight loss (Knowler *et al.*, 2002). It randomly assigned 3,234 individuals without diabetes and with an elevated FPG to a group that received a placebo, metformin (850 mg twice a day) or was given a lifestyle intervention programme. At 3 years, the cumulative incidence of diabetes in the placebo, metformin and lifestyle intervention groups was 28.9%, 21.7% and 14.4%, respectively.

1.5.3 Lipid profile

Blood cholesterol, low density lipoproteins (LDL) and triglycerides all occur at high levels in the serum of individuals who are obese (Jebb *et al.*, 2011). Overweight individuals usually have reduced levels of high density lipoproteins (HDLs) and there is generally an increased level of triglyceride in those who are insulin resistant. The main recommendation for improvement of lipid profile in patients who are also obese is weight loss (Graessler *et al.*, 2009). However, the issue regarding the impact of weight loss on HDL concentration has been extensively debated, with HDL blood levels being higher in the case of individuals who maintain a stable weight than those who lose weight. This is because all lipids levels fall during weight loss and increase once the weight stabilises.

Poobalan *et al.* (2004) systematically reviewed 13 studies conducted in various countries and concluded that lipid levels, particularly LDL and total cholesterol levels, were favourably impacted in the long-term by weight reduction. In the long-term, cholesterol levels decreased by around 5% (0.23 mmol/l) with an average weight reduction of 10 kg. However, as highlighted by Pi-Sunyer (1996), a weight reduction of 10 kg in the short-term could result in a greater decline in cholesterol levels of up to 10%. Furthermore, the findings obtained by Avenell *et al.* (2004) from systematically reviewing randomised controlled trials (RCTs) indicated that LDL, total cholesterol and triglyceride levels

decreased while HDL levels rose in the case of individuals with overweight or obesity who lost between 5 and 10 kg.

1.5.4 Hypertension

There is a positive correlation between weight changes and blood pressure. According to several studies, blood pressure decreases as a result of weight reduction and enhances blood peripheral resistance by reducing fatty plaques in arteries and capillaries that had obstructed the blood flow. It is suggested that a range of pathophysiological mechanisms may be involved but these have not been identified with certainty. Extracellular volume diminishes as a result of weight reduction and in turn reduces hypervolaemia and cardiac output, inhibits the sympathetic nervous system, reduces resistance to insulin and normalises the correlation between aldosterone and renin, which ultimately leads to the reduction in blood pressure (Mertens and Van Gaal, 2000).

The results obtained by earlier intervention studies revealed that cardiovascular risk factors associated with obesity (e.g. high blood pressure and diabetes) were considerably reduced after intentional weight reduction of 5-10% (Sjostrom *et al.*, 1999). Furthermore, Neter *et al.* (2003) reviewed a series of RCTs and found that, for each kilogramme of weight lost, the diastolic pressure dropped by 0.92 mmHg. The Hypertension Prevention Collaborative Research Group (1992) compared how the diastolic and systolic blood pressures were affected by weight loss among 308 individuals with hypertension and among 256 individuals with normal blood pressure. The hypertensive group lost 23.9 kg (4.3%) following a year and a half of intervention, which caused the diastolic and systolic blood pressures to decrease to 22.3 mmHg and 22.9 mmHg, respectively. Meanwhile, a Look AHEAD study found that the systolic pressure (-5.33 vs. -2.97 mm Hg; p <0.001) and diastolic blood pressure (-2.92 vs. -2.48mmHg; p =0.01) of individuals subjected to an intensive intervention over four years improved more significantly than those in control group (Wing, 2010).

1.6 Therapeutic interventions for obesity

1.6.1 Existing guidelines

The initial step in the treatment of obesity is to identify individuals who are overweight or obese. In the UK and the US, weight management is typically undertaken in the context of primary care, since the numbers of patients who are overweight or obese has become so high (SIGN 8, 1996; Sciamanna *et al.*, 2000). Although awareness about growing levels of obesity is high, measurements are not conducted on a regular basis. According to the findings of an audit conducted in the UK, the recognition of obesity within primary care was inadequate with weight or BMI measurements were included in the medical records of just two-thirds of the patients of forty general practices that indicated they were interested in weight management (Laws, 2004). In the UK, as part of the Quality and Outcomes Framework (QOF) set up in 2006, general practitioners (GPs) are rewarded for recording individuals with a BMI $\geq$30 kg/m^2 who are aged $\geq$16 years. In 2010, in England, it was found that prevalence of obesity according to the standard set in the QOF (10.5%) was lower than the prevalence recorded in the health survey (26.1%); this result may reflect the fact that not all patients were measured or had yet visited their GP (NHS, 2012). In Scotland, the Scottish Intercollegiate Guideline Network (SIGN) guidelines were issued in 2010 to support management of adult obesity within a clinical context. These guidelines include measures for preventing obesity via primary intervention targeted at people of normal weight or within the obesity range.

Weight gain prevention, achievement of weight reduction of 5-10% or more, and improvement of health and risk factors are the goals outlined by SIGN 115 (2010) for weight management in the case of individuals with obesity. Furthermore, the guidelines emphasise that physical exercise, diet modifications, and behaviour management should be integrated in weight management. It is recommended that the BMI should not exceed 25 kg/m^2, diets should be dominated by foods with lower energy density, such as wholegrains, cereals, vegetables and salads, and alcohol consumption should be limited. SIGN guidelines recommend that healthcare professionals should encourage individuals to weigh themselves and consider the patient's willingness to change before offering weight loss interventions. Additional recommendations include the use of medication in support of diet, physical exercise and behavioural modifications in individuals with a BMI $\geq$28 kg/m^2 with comorbidities or a BMI $\geq$30 kg/m^2, after comprehensive consideration of risks and

benefits. Another option that should be taken into account in adult weight management is bariatric surgery (SIGN 115, 2010).

The guidelines for obesity treatment that have been issued by the NICE (2014) specify that every NHS department should play a role in identifying and managing individuals who are overweight or obese. One of the greatest difficulties confronting healthcare practitioners in the UK is ensuring that patients stay physically active. To effectively deal with obesity, a multi-faceted strategy has been advocated by the NICE lifestyle guidelines (NICE lifestyle, 2014). Ijzelenberg *et al.* (2012) advocated the prioritisation of commercial programmes for obesity management such as community-based programmes focusing on healthy eating and physical activity. Additionally, to motivate individuals to improve their lifestyle, cognitive behavioural therapy should also be included in weight management programmes.

An approach integrating physical activity, diet and behavioural changes is considered the most effective in managing obesity and excessive weight. However, bariatric surgery or medication therapy is necessary in the case of some individuals. No treatment is commenced before an assessment of a patient is conducted to determine any potential risks. This so-called "risk-benefit assessment" helps to establish which treatment would be most effective (Neff and le Roux, 2013). The amount of excessive weight and patients' preferences are taken into account when deciding on a specific treatment course.

In conclusion, the NICE (2014) recommend that multicomponent interventions should be the treatment of choice for people with obesity. Patients should be given all the information they need regarding realistic targets for weight loss (5-10% of initial weight) and know that the main requirement to reach the target diet is that energy expenditure should be higher than the total energy intake. In addition, 45-60 minutes/day of physical activity may help to prevent obesity in people who cannot reduce their energy intake; and 60-90 minutes/day of physical activity may be needed for people who are obese and have recently lost weight. Furthermore, the NICE (2014) guidelines recommend drug treatment for patients who have not yet reached their target weight loss through lifestyle interventions and the consideration of bariatric surgery for those with a BMI >50 kg/m^2.

1.6.2 Modifications in lifestyle and physical activity

Weight gain is the result of sedentariness, lack of physical activity, and unhealthy eating patterns. Hence, improving these aspects is the focus of the majority of weight

management programmes (Esposti *et al.*, 2006). Behavioural programmes seeking to improve lifestyle choices are referred to as lifestyle interventions. At the same time, weight management programmes put great emphasis on physical activity as a solution to redress the balance between energy intake and energy consumption. Changes in what individuals eat and drink, how much they eat and drink and how often are necessary to reduce the intake of calories and, thus, to achieve weight reduction. The energy intake should be reduced by 600 kcal/day or 3,500 kcal/week, in order to attain the recommended weight loss of 0.5 kg per week.

Diets with low fat content, modest energy prescription, low or extremely low caloric content, protein-sparing modified fasts, and diets low in both carbohydrates and fat can all help to reduce the energy intake. A range of diets with at least one-year follow-up was compared in the context of a detailed health technology assessment (HTA). In the case of a 600 kcal deficit diet or diet with low fat content, the average amount of weight lost over twelve comparisons was -4.6 kg (95% CI: -7.20 to -0.60 kg), while standard interventions led to an increase in weight of 0.60 kg (95% CI: -1.30 to +2.40 kg) (NICE, 2006; SIGN, 2010). Similarly, at the one-year follow-up, a moderate weight reduction of 5-6% as a result of hypocaloric diets with 800-1800 kcal/day intake and less than 800 kcal/day was recorded by Tsai and Wadden (2006). In a different study, a moderate weight loss of 5 kg was recorded at the one-year follow-up as a result of diets low in carbohydrates (<30 g/day) and low in fats (<30% of overall energy intake from fat per day) (Nordmann *et al.*, 2006). Additionally, the results obtained by Pi-Sunyer *et al.* (2007) in the Look AHEAD study indicated that lifestyle interventions of high intensity led to a 5% weight reduction in 68% of the participants and a minimum of 10% weight reduction in 37% of the participants.

The benefits of physical activity include maintenance of weight reduction in the long-term and maintenance of a lean body mass during dieting. The UK guidelines suggest that, in order to derive health benefits, adult individuals should engage in moderately intense physical activity for a minimum of 150 minutes weekly. However, this interval may need to be prolonged, since the recommendation of 150 minutes was formulated based on physical activity that participants in longitudinal observational studies themselves reported. According to the SIGN guidelines (SIGN 115, 2010), individuals with overweight or obesity issues should aim for 225-300 minutes of moderately intense physical activity per week, which could be completed in five sessions of 45-60 minutes weekly and would result in the burning of 1,800-2,500 kcal/week. Furthermore, physical activity should be

undertaken in conjunction with other strategies of weight management. Jakicic *et al.* (2008) reported that adult female individuals with obesity exhibited a dose-response relationship with regard to the level of physical activity they engaged in and the ability to maintain the weight they lost in the long-term. Hence, to summarise, behavioural therapy, physical activity, and dietary intake represent the three cornerstones through which lifestyle interventions can achieve beneficial changes.

Other study reported that, after one year, greater weight reduction was achieved through an intervention consisting of 45 minutes of physical activity three times a week and a low fat diet aimed at reducing the caloric intake by 600 kcal/day than through a programme consisting of diet alone. The diet-only group achieved an average weight reduction of 4.10 kg (range -4.00 kg to -5.10 kg), while the physical activity combined with dieting group lost on average of -5.60 kg (range -5.10 kg to -8.70 kg) (NICE, 2006). Furthermore, diet alone is not as efficient as an intervention comprising physical exercise, behavioural therapy and hypocaloric diet, as attested by a meta-analysis of five studies, which revealed that diet alone led to a weight reduction of just 0.48 kg (range 0.53 kg to -2.40 kg), while the combined intervention achieved a weight reduction of 4.60 kg (range -3.33 kg to -5.87 kg) (NICE, 2006; SIGN 115, 2010).

The treatment of adult with obesity benefits greatly from behavioural programmes (Shaw *et al.*, 2005) which are designed to bring about changes in the way individuals act and think that are in line with changes in patterns of physical activity and diet. To lose weight and prevent regaining it, individuals must have a range of behavioural skills. Behavioural therapy aims to equip individuals with techniques and practices that will change their attitude to physical activity and eating. Some behavioural change techniques include patient monitoring, motivational enhancement, and cognitive behavioural therapy. It has been demonstrated that, in comparison with diet alone, diet combined with behavioural therapy achieved greater weight reduction after one year.

Shaw *et al.* (2005) indicated that greater weight reduction was achieved through lifestyle interventions focusing on development of healthy eating behaviour coupled with physical exercise than through interventions focusing on just physical exercise or just diet. There are various factors that can determine the extent of treatment success. Thus, treatment success can be diminished by family traits, such as parents with obesity (Sabin, 2007) and/or siblings, attachment avoidance on the part of the mother, as well as maternal depression. Reinehr *et al.* (2010) argued that outcomes after five years could be anticipated

based on BMI decrease during interventions. The processes of weight management can be more comprehensively understood and obesity treatments can be improved once the factors that most favourably and unfavourably affect weight loss are better understood.

1.6.3 Medication-based treatment

The efficiency of medication-based treatments of obesity, either on their own or integrated with behavioural therapy, has been the focus of many studies. The main purpose of medication-based treatments is to regulate food consumption and body weight (Ornellas and Chavez, 2011), particularly in individuals who struggle with maintaining weight reduction through changes in eating habits and lifestyle.

1.6.3.1 Orlistat

Orlistat is used to treat obesity in the long term. It often modifies the digestion of fats by restraining the pancreatic lipases (Heck *et al*., 2000). Hence, fats are not hydrolysed completely and excretion of faecal fat is augmented. This medicine is usually available in 120 mg capsules with the recommended dose being 120 mg to be taken three times daily (Berne, 2005). Orlistat's effectiveness in facilitating weight loss has been verified in various other meta-analyses and randomised trials (Li *et al*., 2005; Torgerson *et al*., 2004).

In numerous other trials related to patients with diabetes, orlistat resulted in a significantly higher of weight loss and diminished glycosylated haemoglobin (HbA1c) at 1 year when compared to the placebo groups (Kelley *et al*., 2002). Yancy *et al*. (2010) conducted another trial, in which 146 patients suffering from obesity (that is, having a BMI of 39.3kg/m^2) were examined. A low-fat diet (less than 30% of routine energy) in combination with orlistat resulted in a loss of weight (9% on an estimate) that was analogous with a low ketogenic carbohydrate diet (originally less than 20g carbohydrates/day). A 1-year trial was conducted at various centres by Miles *et al*. (2002) to evaluate the effects of orlistat. The trial aimed to check the effects of 120 mg orlistat/three times a day versus a placebo in patients who are overweight or obese with type 2 diabetes who were being treated with metformin. At the end of the 1-year treatment, weight loss was significantly greater in the group which was on orlistat than the placebo group. Glycaemic control improved immensely in the group which was treated with orlistat and the HbA1c serum was significantly reduced. Miles *et al*. (2002) concluded that the orlistat treatment was very helpful in reducing weight and improved the control of

glycaemia along with blood pressure and serum lipid levels in patients suffering from obesity and type 2 diabetes who were being treated with metformin.

In another 57-week randomised double-blind placebo-controlled study, 120 mg of orlistat or a placebo was administered orally three times/day together with hypocaloric diet to 391 men and women aged 18 years and over who were suffering from obesity (with a BMI of 28-40 kg/m^2) and type 2 diabetes and who were being treated with oral sulfonylureas (SUs) (Hollander *et al*., 1998). After 1 year of treatment, the mean weight change in the orlistat group and the placebo group was -6.2 ± 0.45% and -4.3 ± 0.49% (p <0.001), respectively. There are numerous clinical trials which indicate that early weight loss is greater and the rate of weight regain is lowered when a patient is treated with orlistat than when they are treated with a placebo and lifestyle changes.

Another controlled trial was conducted to analyse the tolerance levels and effectiveness of orlistat over a 2-year period in participants without diabetes (Sjostrom *et al*., 1999). In the first year, the group which was on orlistat lost more weight than the group which was given the placebo treatment (10.2% [10.3 kg] vs. 6.1% [6.1 kg]). A total of 743 patients from 15 European centres whose BMI was between 28-47 kg/m^2 were included in this trial. 688 patients were treated with 120 mg of orlistat 3 times/day or a placebo for 1 year. By the second year, patients who were on orlistat gained half the weight they had lost back again when compared to the patients on who switched to placebo (p <0.001). The group of patients who switched from the placebo to orlistat during the second year had an additional weight loss of 0.9 kg. Apart from the weight loss, it was observed that the orlistat group showed lesser concentrations of glucose and insulin, lower cholesterol levels, LDL/HDL ratio and LDL when compared to the placebo group.

This study finally confirmed that orlistat, when taken in conjunction with an appropriate diet, promotes a significant loss of weight and lessens the chances of weight gain in patients who are obese over a period of 2 years. When orlistat is taken for more than 2 years, the patient should be closely monitored for adverse events. Further study showed that orlistat, taken at a dose of 120 mg/three times daily in conjunction with a low caloric diet, can reduce weight by 30 % in patients with type 2 diabetes and hypertension (Berne, 2005).

In a 4-year double blind (XENDOS) study of 3,304 patients with overweight, Torgerson *et al*. (2004) concluded that the use of orlistat along with lifestyle changes exhibited better

results when compared to the changes achieved by adjustment to lifestyle alone. The study concluded that orlistat combined with lifestyle changes reduced the incidence of type 2 diabetes. Prospective subjects who participated in the study were advised of the lifestyle changes they had to make and were given either a placebo three times a day or 120 mg of orlistat three times a day. The BMI of the subjects was less or equal to 30 kg/m^2 and they had an impaired percentage of 21% or normal percentage of 79% glucose tolerance. The primary aim was to check the onset of type 2 diabetes and observe whether there were any changes in body weight. The intention of the analysis was to shed light on effective treatment choices. The percentage of the patients who completed the treatment were 52% in the group treated with orlistat and 34% in the group which received the placebo treatment (p <0.0001). The mean weight loss was significantly greater in the orlistat group when compared with the placebo group (-10.6 kg vs. -6.2 kg; p <0.001). At the end of 4 years, the degree of incidence for diabetes in the patients who received the orlistat treatment was 6.2% and 9% in the patients who received the placebo treatment, which corresponded to an overall risk reduction of 37.3% (p =0.003). The mean weight change in the orlistat group and the placebo group was -5.8 kg and -3.0 kg, p <0.001, respectively.

Worldwide, over the past ten years, it is estimated that 40 million individuals were treated with orlistat. Douglas *et al*. (2013) conducted a population-based study using data on acute liver injury incidences from the use of orlistat reported through the "UK Clinical Practice Research Data link". They found that acute liver injury incidences from the use of orlistat augmented (roughly doubled) ninety days before and thirty days after the treatment began in comparison with background prevalence. The data suggested that this linkage is not causal. On the other hand, patients taking orlistat are warned to contact healthcare professionals if they see sign of anorexia, pale coloured stools, jaundice, and itching. In addition, a study reported a statistically significant decrease in the presence of all assessed fat-soluble vitamins after 4 years of treatment in the orlistat group when compared with the placebo group (Torgerson *et al*., 2004).

1.6.3.2 Other drugs

Liraglutide (Victoza®) is a glucagon-like peptide-1 (GLP-1) long-acting analogue. Liraglutide is administered once a day by subcutaneous injection and has shown benefits for glycaemic control at doses up to 1.8 mg/day and for weight loss at doses of up to 3.0 mg once daily (Astrup *et al*., 2012). Its effect is on the gastrointestinal tract and the brain by as it suppresses appetite and energy intake in both normal-weight people and people

with obesity as well as in individuals with type 2 diabetes and it delays gastric emptying (Astrup *et al*., 2009). The fact that liraglutide causes dose-dependent weight loss, decreases the concentration of HbA1c, improves β-cell function and systolic blood pressure (Vilsboll *et al*., 2007) makes it a treatment option for both type 2 diabetes and obesity.

The taking of liraglutide in diabetes trials is linked significantly with weight reductions (2.0 to 2.5 kg). The loss in weight is also observed in people without diabetes receiving liraglutide over a 20-week. Astrup *et al.* (2009) conducted an RCT among 564 participants with a BMI in the range 30-40 kg/m^2. Of these, 95 were distributed at random to one of four liraglutide doses (1.2 mg, 1.8 mg, 2.4 mg, or 3 mg); 98 were allocated to the placebo group; and 95 were allocated to the orlistat 120 mg group. An intervention comprising 500 kcal/day energy-deficit diet and physical exercise was applied to all participants. Results indicated that, by comparison to the placebo (all doses) and orlistat (vs. 2.4 and 3 mg liraglutide), a more significant weight reduction was achieved by liraglutide administered together with lifestyle intervention. The four liraglutide doses led to an average weight reduction of 4.8, 5.5, 6.3 and 7.2, respectively, while the placebo and orlistat induced weight reduction of 2.8 and 4.1 kg. The percentage of individuals who lost more than 5% of their weight in the liraglutide 3.0 mg group was 76% (n =70) when compared with the individuals in the placebo group (30%, n =29) or the orlistat group (44%, n =42).

Moreover, in an earlier RCT (SCALE study) conducted in 27 countries in North America, Europe, Asia, South America, Africa, and Australia from 1 June 2011 to 18 March 2013 (Pi-Sunyer *et al*., 2015), 3,731 participants without diabetes received counselling on lifestyle modification; 2,487 participants received liraglutide 3 mg, and 1,244 participants received a placebo. At week 56, the mean weight change in the people in the liraglutide group was -8.4±7.3 kg and in people in the placebo group was -2.8±6.5. The estimated treatment difference was -5.6 kg (95% CI: -6.0 to -5.1 kg), p <0.001.

Drugs such as phentermine and topiramate (Qsymia®) (not available in the UK, but available in the US) given in combination are an option for obese adult without coronary heart disease and who do not suffer from hypertension (Bays, 2010). Phentermine, a nonselective stimulator of synaptic noradrenaline, dopamine and serotonin release, has been widely used (mainly outside of Europe) as a short-term appetite suppressant since the 1960s (Ryan and Bray, 2013). Topiramate is an anticonvulsant drug and approved for the prophylaxis of migraine headaches. It has shown substantial weight reduction in individuals with obesity but is not currently approved as a treatment for obesity (Garvey *et*

al., 2012). The US FDA in 2012 approved an extended-release topiramate and phentermine preparation (in one capsule) for adults having a BMI ≥27 kg/m^2 along with at least one comorbidity related to obesity or a BMI ≥30 kg/m^2 (e.g., dyslipidaemia, diabetes and hypertension) (Gadde *et al*., 2011). Such a combination was thought to increase the loss in weight in the initial year of use, as was demonstrated by the subsequent trials:

In a CONQUER study (Gadde *et al*., 2011), the phentermine-topiramate combination and its controlled release (15/92 mg or 7.5/46 mg) was compared with the placebo in 2,487 adults having a BMI of 27 to 45 kg/m^2 and two or more comorbidities. After one year, the mean weight loss was -1.4 kg (95% CI -1.8 to -0.7 kg) in the placebo group, -8.1 kg (95% CI: -8.5 to -7.1 kg; p <0.0001) in the group given 7.5 mg of phentermine and 46 mg of topiramate and -10.2 kg (95% CI: -10.4 to -9.3; p <0.0001) in the group given 15 mg of phentermine and 92 mg of topiramate. Only 61% of the participants successfully completed the 1 year treatment, which raised questions regarding the outcomes of the trial.

In the SEQUEL study (Garvey *et al*., 2012), which was a 52 week extension of the CONQUER study, around 676 (78%) of the participants participated in the trials. The results showed a significant mean weight loss than the placebo group (108 weeks of baseline data) with a loss of -2.1 kg, -9.6 kg, and -10.9 kg in the placebo, 7.5 mg phentermine / 46 mg topiramate, and 15 mg phentermine / 92 mg topiramate groups, respectively (p =0.0001). Hence, phentermine-topiramate treatment proved to be less effective in enhancing weight loss in the second year, but a number of participants were able to maintain the weight lost in one year.

The combination of bupropion and naltrexone (Contrave®) was evaluated successfully in various clinical trials. Naltrexone is a pure opioid antagonist and bupropion is an antidepressant of a dopamine reuptake inhibitor. In a RCT including naltrexone and bupropion versus double placebo, the loss in weight was enhanced in individuals assigned to treatments given actively (with a mean weight change of -1.3% in the placebo group, -6.1% in the naltrexone 32 mg/ bupropion group (p <0.0001) and -5.0% in the naltrexone 16 mg / bupropion group (p <0.0001)) (Greenway *et al*, 2010).

Lorcaserin (Belviq®) also known as Lorqess is an optional treatment with an efficacy that is comparable to orlistat. It was officially launched in the USA in June 2013 (Manning *et al*., 2014). It is a selective serotonin 2C receptor agonist that could be useful in reducing body weight. It causes less adverse effects when compared to orlistat but information on its

safety in the long-term is limited. In one a long running RCT 3,182 adults who are obese with a BMI of 30–45 kg/m^2 or 27–45 kg/m^2 and at least one weight related comorbidity were randomised to receive lorcaserin 10 mg twice daily or a placebo twice daily (Smith *et al*., 2010). These participants also took part in programmes on lifestyle adjustment related to exercise and nutritional counselling.

The average weight loss was 5.8±0.2 kg in individuals taking lorcaserin and 2.2±0.1 kg in individuals taking the placebo during year 1 (p <0.001). In the second years, the placebo group patients continued to get the placebo, while the lorcaserin group patients were reassigned randomly to receive either the placebo or lorcaserin. In one year, the individuals receiving lorcaserin successfully lost 5% or more of their baseline body weight and the majority of the patients who had received lorcaserin during the 2 years maintained their loss in body weight (67.9 vs. 50.3%, p <0.001). After two years, the participants who had been reassigned to the placebo had gained the weight back.

1.6.4 Surgical intervention

Most individuals fail to reach their weight reduction goal only through lifestyle interventions, despite the fact that diet and physical activity are undoubtedly important in the treatment of obesity (Tuah *et al.*, 2011). As reported by Douketis *et al.* (2005), individuals lost less than 5 kg after 2-4 years of dietary and lifestyle interventions, whereas the amount of weight lost after 1-2 years of medication-based treatment was 5-10 kg and the greatest weight reduction of 25-75 kg was achieved after 2-4 years as a result of surgery. Individuals with obesity can reduce their weight most effectively through bariatric surgery, including the Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB) and sleeve gastrectomy (SG) (Buchwald and Oien, 2009). In the case of the morbidly obese, biliopancreatic diversion is the optimal method of bariatric surgery (Smith *et al.*, 2008); however, no one does this operation in the UK as it can be very dangerous.

According to the SIGN guidelines (SIGN 115, 2010), bariatric surgery ought to be incorporated in a general clinical approach for weight management intended for adults. Following subject evaluation of risk-benefit, several conditions must be met by individuals to qualify for bariatric surgery, including:

- BMI equal to or greater than 35 kg/m^2.

- Development of at least one serious comorbidity (e.g. arthritis and type 2 diabetes) that could be significantly improved through weight loss.
- Proof of completion of a weight management programme combining dieting, physical exercise, behavioural therapy, and medication-based treatment, but without success in alleviating comorbidities.

O'Brien *et al.* (2006) conducted an RCT among 80 participants who had a BMI of 30-35 kg/m^2 and displayed morbidities associated with obesity. Results showed that, at 24 months, greater weight reduction was achieved with the adjustable gastric banding than with an intensive intervention comprising diet, lifestyle changes and medication-based treatment (87.2% vs. 21.8%, p <0.001). In a different study, Dixon *et al.* (2008) reported that the greater weight reduction achieved through surgery contributed significantly to improvement of type 2 diabetes. At the 24-month follow-up of 60 individuals, the group assigned surgery had accomplished an average weight reduction of 20.7%, with 73% of individuals in this group achieving type 2 diabetes improvement. By contrast, the group assigned standard treatment achieved an average weight reduction of 1.7%, with 13% of the individuals in this group exhibiting type 2 diabetes improvement. Furthermore, Colquitt *et al.* (2005) also found that, at the 24-month follow-up, the likelihood of hypertriglyceridemia and low HDL cholesterol was more diminished as a result of bariatric surgery than as a result of the most effective non-surgical weight management programme. In their RCT conducted on 150 individuals, Schauer *et al.* (2012) confirmed that, at the 12-month follow-up, the medical therapy group (-5.4±8.0 kg) had not achieved the level of weight reduction achieved by the gastric bypass (-29.4±9.0 kg) and the sleeve gastrectomy (-25.1±8.5 kg) groups. Moreover, the systematic review undertaken by Vest *et al.* (2012) indicated that bariatric surgery not only diminished risk factors associated with cardiovascular disease, but also improved left ventricular hypertrophy and diastolic function.

1.7 The impact of weight management services

The NHS Commissioning Board issued recommendations on the clinical commissioning for specialised obesity surgery, which introduced different tiers of weight management services. Tier 1 usually covers universal services such as primary care; tier 2 includes lifestyle interventions; tier 3 covers specialist weight management programmes; and tier 4 includes bariatric surgery (NHS Commissioning board, 2013). The NICE guidelines recommend multi-component lifestyle interventions, including diet, physical activity and behavioural change, as the treatments of choice for obesity (NICE, 2014).

The NICE (2014) has recommended a number of programmes for obesity treatment that are offered by different health management agencies throughout the UK. To ensure value for money, programmes must produce long-term weight loss results rather than just temporary weight loss. However, the outcomes accomplished by different group-based projects available in the UK have not been long-lasting. A series of recommendations have been formulated by NICE (2014) for the local authorities responsible for liaising with clinical commissioning bodies, local healthcare providers, and health and wellbeing boards. Lifestyle change and health education are the focus of these recommendations and the active participation of health and medical professionals, including pharmacists, general practitioners (Jolly *et al.*, 2011) as well as health visitors and community health officers, is advocated. Among the recommendations made are the implementation of a comprehensive strategy of obesity prevention and management. This would offer assurance of service safety, dissemination of information about local weight management programmes via the commissioners, introduce different strategies from health and social care practitioners to promote lifestyle intervention services, and disseminate information about available obesity and health management programmes. Such information would include the option of referral for individuals with overweight and obesity to the relevant health intervention programmes, and the promotion of practices and techniques to assist individuals to improve their motivation and adopt a more positive attitude towards healthy eating and a healthier lifestyle (Jebb *et al.*, 2011).

Numerous providers of weight management programmes exist in the UK and access to these programmes can be secured via the National Health Service (NHS) or commercial sources. Commercial weight management programmes require payment to provide assistance and help with weight loss.

A number of commercial weight management programmes are currently available in the UK, including Weight Watchers, Slimming World, and the Rosemary Conley programmes. These group-based programmes allow participants to join at any time. Each programme combines individual support with group discussion that is overseen by the programme leader. Generally, meetings last between 60 minutes to one and a half hours and are organised in community spaces. The whole structure of these programmes revolves around the reduction of energy intake by 600 kcals per day and to achieve a weekly weight reduction of 0.5-1 kg. In addition, these programmes include support to increase physical activity and behavioural modification. For every 3.2 kg lost and at the 5% and 10% of body weight loss target, the participants receive rewards.

Most of the available evidence obtained to date has resulted from the evaluation of the tier 2 weight management. However, the NHS Glasgow and Clyde Weight Management Service (GCWMS) is a tier 3 weight management service available in the UK that will be assessed in this study. The different studies that assessed various weight management programmes are listed in **Table 1-5**. Included are the studies conducted by Morrison *et al.* (2011) and Logue *et al.* (2014) that discussed the results of the GCWMS in 2011 and 2014, respectively. The search for these studies was conducted on 2 January 2017, and was limited to studies published between January 2007 and December 2016. Search terms such as weight management, weight loss, programme, tier 2, tier 3, obesity management, and intervention were applied to the Ovid database. A manual search was also conducted, and certain studies were included based on colleagues' recommendations.

Study, Author and Year	Study Population	Methods and interventions	Results
1- Specialist health visitor-led weight management intervention in primary care: exploratory evaluation**.** **(*Jackson et al., 2007)***. (Tier 2).	Individuals with a BMI ≥30 kg/m^2.	Weight management clinic managed by specialist health visitors in the context of primary care. Collection of clinical outcome data and data about self-reported food intake was undertaken at weeks 1, 13, 27 and 52. Collection of quantitative and qualitative data regarding patients' satisfaction with the clinic was undertaken at week 26.	Clinic attendance included 89 individuals. In the long-term, there was a reduction in average body weight and BMI. About one in ten individuals had diabetes that was not diagnosed. There was a statistically significant reduction in the average self-reported intake of cakes, desserts and snacks and an increase in the intake of fruit and vegetables per week. The clinic was deemed highly satisfactory by the patients, and they considered that the contribution of the specialists health visitors as being especially valuable.
2- Planning to lose weight: randomised controlled trial of an implementation intention prompt to enhance weight reduction among overweight and obese women. **(*Luszczynska et al., 2007)***. (Tier 2).	Individuals in the age group 18-76 years old, with a BMI greater than 25 kg/m^2 were included. The average weight and average BMI were 89 kg and 33.3 kg/m^2, respectively.	The control and weight groups consisted of 29 and 27 participants, respectively. The conditions involved watchers with implementation intention prompt (IIP) and the programme lasted for two months.	Control: -2.1 kg (95% CI: 1.11-3.09), -2.4% IIP: -4.2 kg (95% CI: 3.19-5.07), -4.7%
3- Evaluation of the Counterweight Programme for obesity management in primary care: a starting point for continuous improvement. **(*Counterweight Project Team, 2008)***. (Tier 2).	1906 individuals with BMI ≥30 kg/m^2 or BMI ≥28 kg/m^2 and obesity-associated morbidities.	Prospective appraisal of a novel ongoing improvement framework for weight management in the context of primary care. Weight change and proportion of individuals losing at least 5% of their body weight at one and two years represented the primary outcome measures.	Average weight loss at one and two years was respectively -3.0 kg (95% CI: -3.5 to -2.4 kg) among 642 individuals and -2.3 kg (95% CI: -3.2 to -1.4 kg) among 357 individuals. Weight loss of clinical significance was achieved and maintained with this intervention in the context of routine primary care.
4- Process evaluation of an internet-based resource for weight control: use and views of an obese sample. **(*MCconnon et al., 2009)***. (Tier 2).	A number of 221 individuals from Leeds, UK, in the 18-65 years age group and with a BMI ≥30 kg/m^2. They could access the Internet one or more times weekly and were English literate.	Weight control website active for one year. Collection of data was undertaken at baseline, half a year and one year in the context of a community-based RCT and the data were used for questionnaire-based assessment.	At half a year, 59 individuals (53%) indicated that they had used the website, while at one year, 32 of them (29%) stated website usage. Regarding promotion of favourable behaviour change for weight regulation, a marginally negative score was obtained.
5- Evaluation of attendance and weight loss in an intensive weight management clinic compared to standard dietetic care. **(*Hickson et al., 2009)***. (Tier 2).	Individuals with obesity participating in an intense weight management clinic (IWMC) or a general dietetic outpatient clinic.	Collection of data was undertaken from consecutive individuals suffering from obesity who participated in an IWMC or general dietetic outpatient clinic.	There was no significant difference between clinics in terms of weight loss rate. The intensive clinic achieved an average weight loss of 1.8% as indicated by the final recorded weight, whereas the general clinic did not achieve any overall weight loss.
6- Primary care referral to a commercial provider for weight loss treatment versus standard care: a randomised controlled trial (Lancet),	772 individuals (668 female and 104 male) 18 years of age or older with a BMI of 27-35 kg/m^2. Average weight and average BMI	Primary care practices situated in Germany, Australia and the UK. The commercial Weight Watchers programme and standard care involved 378 and 395 participants, respectively, and lasted for one year.	Weight loss achieved in the commercial programme and standard care was -5.06 kg (-5.8%) and -2.25 kg (-2.6%), respectively (p <0.0001).

(*Jebb et al., 2011)*. (Tier 2).	were 86.7 kg and 31.4 kg/m^2, respectively.		
7- Comparison of range of commercial or primary care led weight reduction programmes with minimal intervention control for weight loss in obesity: Lighten Up randomised controlled trial. **(*Jolly et al., 2011)***. (Tier 2).	740 participants (495 female and 245 male) were all 18 years of age or older. Caucasian Europeans, regardless of ethnicity, had a BMI ≥28 kg/m^2 with comorbidities or BMI ≥30 kg/m^2 without comorbidities. South Asians had BMI ≥23 kg/m^2 with comorbidities or BMI ≥25 kg/m^2 without comorbidities. Average weight and average BMI were 93.3kg and 33.6 kg/m^2, respectively.	Interventions took place at 17 primary care practices in South Birmingham, England. The programmes Weight Watchers (WW), Slimming World (SW), Rosemary Conley (RC), Size Down (SD), and Choice and Comparator (C) all had 100 participants each. The general practice (GP) and pharmacy (P) groups each included 70 participants. The interventions lasted for three months.	WW: -4.4 kg (95% CI: 3.6 to 5.3), -4.7% SW: -3.6 kg (95% CI: 2.7 to 4.4), -3.8% RC: a -4.2 kg (95% CI: 3.2 to 5.2), -4.5% SD: -2.4 kg (95% CI: 1.7 to 3.1), -2.5% Choice: -3.3 kg (95% CI: 2.5 to 4.1), -3.6% C: -2 kg (95% CI: 1.2 to 2.8), -2.1% GP: -1.4 kg (95% CI: 0.4 to 2.3), -1.5% P: -2.1 kg (95% CI: 1.0 to 3.2), -2.3%
8- Weight Watchers on prescription: An observational study of weight change among adults referred to Weight Watchers by the NHS. **(*Ahem et al., 2011)***. (Tier 2).	29,560 individuals enrolling in the Weight Watchers programme during 2 April – 6 October 2009 via the Weight Watchers NHS Referral Scheme.	Observational study for the purpose of measuring weight loss upon completion of twelve sessions. Medians and inter-quartile ranges (IQR) were used to represent the data.	The median weight change among the participants was -2.8 kg [IQR -5.9 - -0.7 kg]. A weight reduction ≥5% was achieved by 33% of all course, while a minimum of 5% weight loss was accomplished by 57% of participants who completed the programme.
9- Evaluation of the first phase of a specialist weight management programme in the UK National Health Service: prospective cohort study. **(*Morrison et al., 2011)***. (Tier 3, NHS).	Individuals with BMI ≥35 kg/m^2 or BMI ≥30 kg/m^2 with comorbidities who had received referral to the GCWMS during the period 2004-2006.	The specialist weight management programme GCWMS To estimate probability of weight loss ≥5 kg in all participants and those who completed the programme as well as the probability of completion (95% confidence intervals), multiple logistic regression analysis was applied in a prospective cohort study.	Weight loss ≥5 kg was achieved by 35.5% of the 809 participants who completed the programme. Men 40 years of age or older, with a BMI ≥50 kg/m^2 and suffering from depression were more likely to lose ≥5 kg. Factors detrimental to weight loss were diabetes mellitus and low socioeconomic status. Participants 40 years of age or older, with a BMI ≥50 kg/m^2 were also more likely to complete the programme. Participants of low socioeconomic status were less likely to continue with the programme until the end, hence their probability of losing ≥5kg was limited.
10- Attendance and weight outcomes in 4754 adults referred over 6 months to a primary care/commercial weight management partnership scheme. **(*Stubbs et al., 2012)***. (Tier 2).	575 male and 4,179 female participants enrolled in a Slimming World programme via referral scheme during the period May 2004-November 2009.	The Slimming World programme consisted of 24 weekly sessions.	Male participants lost more weight than female participants ($p <$ 0.001). A weight reduction of 5% or more was achieved by 74.5% of the total number of participants and by 79.3% of participants who attended at least 20 sessions. A 10% weight reduction was achieved by 37.3% of the total number of participants.
11- Weight loss and dropout during a commercial weight-loss program including a very-low-calorie diet (VLCD), a low-calorie diet (LCD), or	9,037 participants joined the Itrim weight loss programme during the period 1 January 2006 – 31 May 2009.	Observational cohort study that established a correlation between commercial weight loss data and the National Health Care Registers. Participants were allocated to three groups: VLCD =500 kcal formula, LCD =1200-1500 kcal	The VLCD, LCD and restricted normal diet groups achieved a weight loss of 11.4 kg, 6.8 kg, and 5.1 kg, respectively, at twelve months. Participants were more likely to withdraw from the programme if they were younger and did not lose much weight

restricted normal food: observational cohort study. (***Hemmingsson et al., 2012)***. (Tier 2).		formula and restricted normal diet =1500-1800 kcal/day.	initially (p =0.001).
12- Outcomes of a specialist weight management programme in the UK National Health Service: prospective study of 1838 patients. (***Logue et al., 2014)***. (Tier 3, NHS).	Individuals with BMI ≥35 kg/m^2 or BMI ≥30 kg/m^2 with comorbidities who were referred to the GCWMS during 2008-2009	Structural educational lifestyle programme combining cognitive behavioural therapy, 600 kcal reduction per day, physical activity instructions, hypocaloric diet and medication-based treatment. The prospective observational study employed LOCF and BOCF to report average weight loss of 5 kg and 5% weight reduction for all participants and those who completed phase 1, phase 1+2 and phase 1+2+3.	The proportions of participants who lost ≥5 kg by the end of phase 1, phase 2, and phase 3, respectively, were 26%, 30%, and 28%. Male participants, especially those who were 29 years of age or younger, lost a greater amount of weight.
13- A community pharmacy weight management programme: an evaluation of effectiveness. **(*Morrison et al., 2013)***. (Tier 2).	Participants were selected from among individuals living in Fife region, Scotland, with a BMI ≥30 kg/m^2 or a BMI ≥28 kg/m^2 with comorbidity, who did not have access to the Counterweight programme via GP practices.	Community pharmacies that had received training and relevant materials from Counterweight consultants provided the Counterweight programme. During each session, pharmacy personnel weighed each participant, and the documented weight data enabled estimation of weight loss and attendance at 3, 6, and 12 months.	A weight reduction ≥5% was accomplished by 32 of the 314 participants (41.6%, 4.1 kg average weight reduction) who attended the programme for a minimum of one year. Application of the Last Observation Carried Forward indicated that, within a year of joining the programme, the target weight reduction was accomplished by 15.9% of participants
14- Evaluation of a multidisciplinary Tier 3 weight management service for adults with morbid obesity, or obesity and comorbidities, based in primary care. **Fakenham. (*Jennings et al., 2014)***. (Tier 3, NHS).	230 individuals 18 years of age or older with BMI ≥40 kg/m^2 or BMI ≥30 kg/m^2 comorbidity.	The purpose of the cohort study was to assess the FWMS. The goal was to achieve 5% weight loss at one year for all participants and 5% weight loss at half a year for 50% of participants.	Of the 170 participants whose weight was measured at one year, weight reduction of ≥5% was achieved at three months by 25.2% of them, at six months by 44.1%, at nine months by 59.1%, and at one year by 60%. Programme completion was achieved by 117 participants, and of these, weight reduction >5% was achieve at three months by 34.2%, at six months by 53.8%, at nine months by 65.8%, and at one year by 72.6%.
15- Evaluation of the 'Live Life Better Service', a community-based weight management service, for morbidly obese patients. **(*Wallace et al., 2016)***. (Tier 2).	Individuals living in Derbyshire, UK, who were morbidly obese, with BMI >40 kg/m^2 or BMI ≥35 kg/m^2 with comorbidities.	Mean weight loss was calculated based on a one-group pre-post design. Measurements were conducted at baseline, 12 weeks, 24 weeks, 12 months, 18 months and 24 months, and the paired sample t-test gave the significance (p ≤0.05).	Participants who were committed to the programme achieved a weight reduction of statistical significance at 3 months and 24 months of 4.9 kg and 18.2 kg, respectively.
16- An evaluation of a multi-component adult weight management on referral intervention in a community setting. **(*Birnie et al., 2016)***. (Tier 2).	559 individuals 18 years of age or older, living in South Gloucestershire, UK, with a BMI ≥30 kg/m^2 or BMI ≥28 kg/m^2 with comorbidities.	A community-based multidimensional weight management programme for adults lasting for three months and combining diet Weight Watchers (WW), physical activity (Exercise on Prescription, EOP) and behavioural change (motivational interviewing).	Average weight reduction was 3.7 kg, the greater amount of weight (5.9 kg on average) being lost by participants who completed the programme. These participants achieved 5% weight reduction in a greater proportion (58%) than those who did not complete the programme (19%) and those who followed only the WW or EOP component (19%).

Table 1-5 Studies evaluating different weight management programmes.

1.7.1 Tier 2 weight management programme

Developed on the theoretical framework of Evidence-Based Quality Assessment, the Counterweight programme is a weight management programme that is intended for people with obesity and delivered within primary care settings by trained primary care and pharmacy support personnel. There are four stages to this programme, namely, practice audit, evaluation of needs, practice support and training, and practice patient intervention and assessment led by nurses (Laws, 2004). The programme is managed by weight management consultants and dieticians, who provide expert support for obesity management, relevant materials, as well as training for nursing staff from 65 general practices in the UK. Patient education based on published materials is provided by practice nurses over the course of nine sessions spanning one year following the preliminary screening. The first-line interventions consist of six one-to-one sessions of up to half an hour long focusing on the formulation of a customised eating plan or six group sessions lasting 60 minutes each, which are organised over a period of 3 months and focus on the setting of goals. Follow-up is undertaken at 6, 9, 12, and 24 months, with the overall goal being reduction of food intake by more than 500 kcal a day.

The programme targets individuals with a BMI $\geq$30 kg/m^2 or with a BMI $\geq$28 kg/m^2 and a comorbidity. The established weight loss goal over nine sessions spanning one year is more than 5% of body weight. A proportion of 31% of participants achieve this weight loss goal, having started from an average BMI of 37 kg/m^2. Hence, by comparison to participants who do not complete the programme, those that do have a greater likelihood of attaining a clinically significant weight reduction of 5% or more. Programme completion requires attendance to at least four sessions over three months, at least five sessions over half a year or at least six sessions over a year.

A comparison of the weight reduction results achieved after one year by the Weight Watchers programme and standard GP care was undertaken across the UK, Australia and Germany. The participants were all 18 years of age and older and had a BMI of 27-35 kg/m^2 and one or more risk factors for comorbidities (Jebb *et al.*, 2011). At baseline, the average BMI was 31 kg/m^2 and a weight reduction equal to or greater than 5% was attained by a proportion of 60% of the participants who completed the programme (McCombie *et al.*, 2012).

Jolly *et al.* (2011) reported on the Lighten Up study, which included participants recruited via welcome letters distributed by GPs. These participants were randomly allocated to one of three commercial programmes, namely, Weight Watchers, Slimming World or the Rosemary Conley programme, or were alternatively allocated to a weight management programme delivered by the NHS. At baseline, the average BMI in this study was 33.8 kg/m^2 and the primary results were delivered upon completion of the first three months, while the achieved weight reduction was reported at the end of 12 months. Ethnicity and occurrence of comorbidities were the criteria applied to recruit participants. Participants without comorbidity were selected if their BMI was $\geq$30 kg/m^2, while participants of South Asian ethnicity were recruited even if their BMI was lower. The findings implied that, out of the other commercial programmes and primary care interventions, the Weight Watchers programme was the only programme to lead to a weight reduction of clinical significance. More specifically, the primary care programme determined weight reduction in 15.7% of participants, while the Weight Watchers programme achieved weight reduction in 31% of participants.

The importance of session attendance to successful weight loss was highlighted by the fact that the Weight Watchers programme had higher attendance rate when compared to the primary care programme. The studies differed in terms of how they reported the programme results, how they gathered data and how they addressed the issue of absent data. In the case of the Weight Watchers study, the average weight loss achieved by participants with overweight and obesity recruited via primary care services was reported at one year, while the Last Observation Carried Forward (LOCF) was employed to deal with absent data. On the other hand, in the case of the Lighten Up study, weight reduction was reported from baseline to programme completion and the final weight achieved was reported on the basis of participants' self-reporting.

Age, sex, deprivation and baseline weight are among the factors that can affect attendance or weight reduction in the context of group-based weight management programmes, therefore affecting the overall success of the programmes. However, Kim *et al.* (2007) did not find weight reduction to be affected by age (p =0.7), sex (p =0.3) or initial weight (p =0.7). By contrast, a study that assessed the Counterweight programme observed that a greater amount of weight was lost by individuals in the 35-44 year age group, which was of statistical significance (Counterweight Project Team, 2008). The study further reported that the average amount of weight loss among women (-2.8 kg; 95% CI: -3.3 to -2.2 kg) was lower than the average amount lost by men (-3.4 kg; 95% CI: -4.5 to -2.3 kg).

Although observed difference was implied by the 95% CIs overlap, no statistical significance was obtained. In a different study, Lloyd and Khan (2011) examined the determinants of effective weight reduction achieved by individuals with a BMI equal to or greater than 28 kg/m^2 who participated in the Healthy Choices Programme organised in Dorset, UK, during the period 1 October 2008 to 30 September 2009. Weight reduction greater than 5% was achieved by participants of 45 years of age or older and weight reduction was more successful among participants with a BMI of 30-34.9 kg/m^2 (class I) that the other classes of overweight or obese individuals.

The weight loss achieved by participants in the Counterweight programme provided by community pharmacies was examined by Morrison *et al.* (2011), who found that, at one year, by using the Baseline Observation Carried Forward (BOCF) the average weight reduction of 314 participants was 1.01 kg and about 10.2% of participants had lost 5% of body weight. By contrast, the findings of a Lighten Up study regarding the weight loss among participants in a weight management programme delivered by pharmacies indicated that, at one year, the average weight loss by using the BOCF was 1.19 kg and 14.3% of participants had lost 5% of their body weight.

1.7.2 Tier 3 weight management programme

In regards to tier 3 weight management services, individuals aged 18 years or older, with a BMI ≥40 kg/m^2 or with a BMI ≥30 kg/m^2 with comorbidity received referral from GPs or practice nurses for participation in a multidisciplinary tier 3 Fakenham weight management service (FWMS) delivered in primary care settings. The purpose of this programme was to achieve a weight reduction of 5% in all participants at one year and to achieve this reduction at half a year in the case of half of the participants. The Tier 3 interventions included are clinical evaluation, medication-based treatment, low-energy liquid diets (LELDs), psychological therapy and bariatric surgery (Jennings *et al.*, 2014). The programme was twelve months long and the 17 patients recruited for the programme had been referred through the individual funding request (IFR) procedure, with the same intervention being applied over a period of half a year. The twelve-month programme encompassed 10-15 sessions, while the six-month programme comprised 9-15 sessions. Participants completing the full programme had an average BMI of 44.1 kg/m^2, while the IFR participants had an average BMI of 49.9 kg/m^2. At half a year, a weight loss of 5% was achieved by 44.1% of the full programme participants and by 53.8% of the completers, while at twelve months, 5% weight reduction was achieved by 60% of the full

programme participants and by 72.6% of the completers. Based on these results, the study confirmed that, by contrast to other services in primary care settings, a Tier 3 weight management programme was the most adequate for individuals who are obese with complex comorbidity.

1.8 The impact of anti-diabetic medication on weight change

The main features of the metabolic disorder of type 2 diabetes mellitus are reduced sensitivity to insulin and gradually rising glucose levels due to the disruption of beta cell function. According to the WHO, diabetics usually display levels of fasting plasma glucose (FPG) equal to or greater than 7 mmol/l and levels of venous plasma ≥11.1 mmol/l at 120 minutes following a glucose load comprising 75 g anhydrous glucose dissolved in water.

The suggested cut-off point for diabetes diagnosis is 48 mmol/l HbA1c. Regulation of glucose as much as possible and prevention of macro- and micro-vascular complications are the major objectives of type 2 diabetes treatment (UKPDS, 1998). Blood glucose can be regulated with various types of drugs, some of which can cause weight reduction or weight gain (Hollander, 2007). The manner in which these drugs act is explained below.

Biguanides: This class of drugs decreases glucose production and glycogenolysis by reducing the resistance of peripheral and hepatic tissues to insulin **(Figure 1-3)**.

SUs: This class of drugs binds to a particular SU receptor to stimulate pancreatic β cells to produce more insulin (Figure 1-3). As a result, the negative energy balance from glycosuria is reversed by glycaemic control, or else the levels of glucose in the blood are lowered, generating a feeling of hunger.

Thiazolidinediones (TZDs): This class of drugs reduces the resistance of hepatic and peripheral tissue to insulin as a way of mediating its function (Figure 1-3). The rise in plasma volume determined by TZDs may lead to weight gain.

Dipeptidyl peptidase-4 (DPP-4) inhibitors: This class of drugs suppresses the DPP-4 enzyme and defers the breakdown of glucagon-like peptide-1 (GLP-1), thus prolonging the action of glucose-based insulin production. Inhibition of the discharge of pancreatic glucagon and decrease of hepatic glucose synthesis are also achieved by this class (Figure 1-3).

GLP-1: This class of drugs promotes insulin production, insulin gene expression and the maturation of pancreatic β cells, whilst also counteracting the incretin effect that causes insulin to be produced in larger quantities after glucose is orally administered (Bosenberg

and Van Zyl, 2008). Gastric emptying suppression or reduction of calorific intake through the central nervous system may occur, resulting in weight reduction.

α-Glucosidase Inhibitors: This class of drugs suppresses several gut enzymes, thereby deferring polysaccharide disintegration, and lowers the levels of postprandial glucose, which leads to a drop in postprandial concentrations of insulin (Bosenberg and Van Zyl, 2008). Digestion of carbohydrates is suppressed and gastric emptying is postponed through GLP-1, which may result in weight reduction.

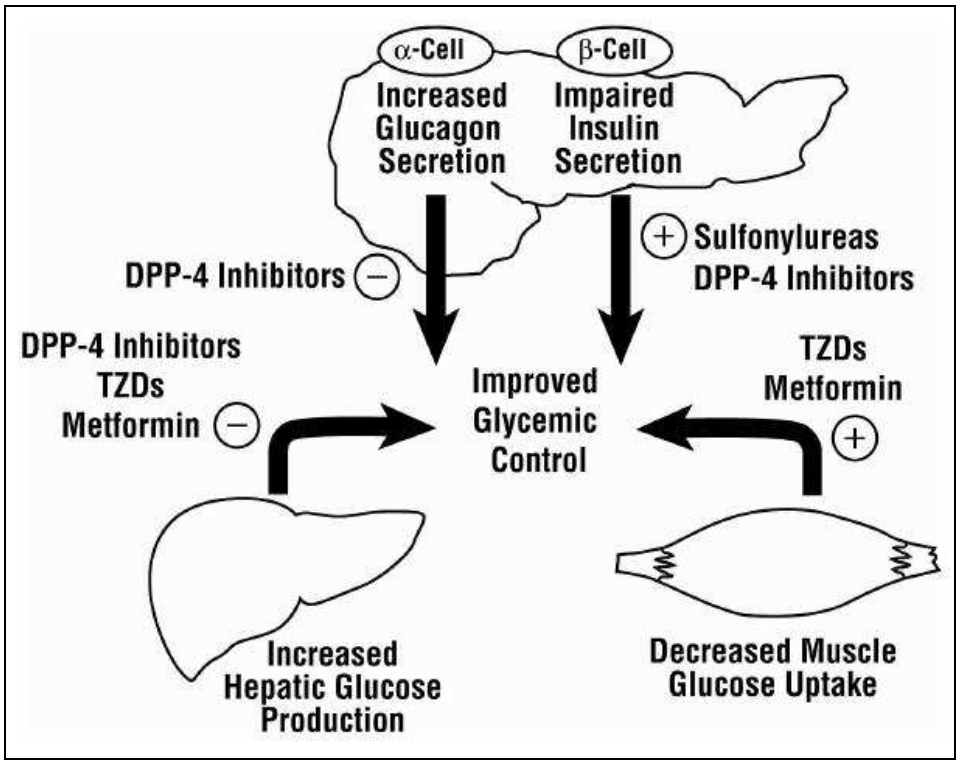

Figure 1-3 Mechanism of action of biguanides, SUs, DPP-4 inhibitors and TZDs (plus=stimulation, minus=inhibition) (DeFronzo, 1999). "Reproduced from the American College of Physicians with permission". License number: 4073791152037.

Sodium/glucose co-transporter 2 inhibitors (SGLT2): A novel class of oral anti-diabetic medication that have been available since 2013; these drugs enhance elimination of urinary glucose without dependence on insulin production or activity, thereby lowering hyperglycaemia (Kim and Chung, 2014) **(Figure 1-4)**. NHS Scotland has approved dapagliflozin for use in some type 2 diabetics and the US Food and Drug Administration (FDA) has approved the use of canagliflozin. By intensifying elimination of renal glucose, these drugs promote calorie consumption and hence may result in weight reduction (Van Gaal and Scheen, 2015).

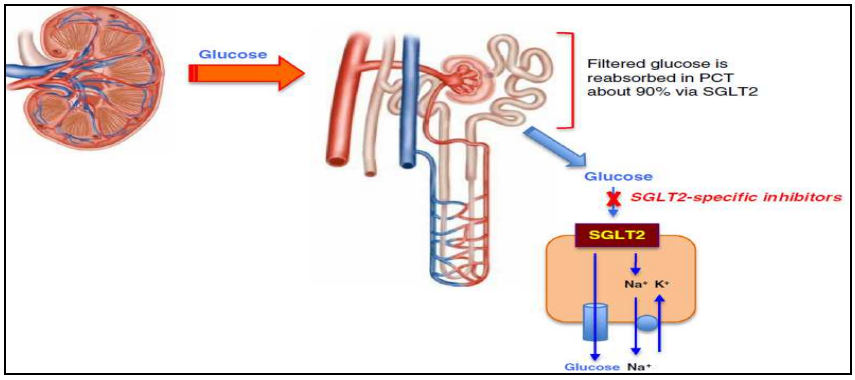

Figure 1-4 Mechanism of action of SGLT2 (Kim and Chung, 2014). "Reproduced from Springer with permission". License number: 4060400726094.

Individuals who are overweight or obese and have type 2 diabetes should be first and foremost prescribed anti-diabetic medication that either contributes to weight reduction or does not affect weight at all. The American Diabetes Association (ADA) and the European Society for the Study of Diabetes (EASD) have developed an algorithm for hyperglycaemia management in type 2 diabetics that gives due consideration to the impact of drugs on weight. According to the SIGN 116 (2010) and ADA/EASD (Inzucchi *et al.*, 2015) recommendations, if metformin proves inefficient in regulating glycaemia or is contraindicated for individuals with overweight and obesity, then GLP-1 and DPP-4 inhibitors should be used (Bonora, 2007). By contrast, Hollander (2007) argued that glycaemic control rather than weight change should be the main priority of the algorithm for type 2 diabetes management. Weight is beneficially influenced by metformin, which is thus suggested as the first choice of medication to be prescribed for individuals with type 2 diabetes.

Metformin should be used together with insulin, SU or a TZD as a second stage in the management of type 2 diabetes, since every one of these drugs causes an increase in weight. On the other hand, weight is reduced or left unchanged by DPP-4 inhibitors and GLP-1 analogues (Phung *et al.*, 2010). There is ample evidence in support of the fact that certain anti-diabetic medication can either increase or decrease weight. Phung *et al.* (2010) reviewed a series of RCTs and found that the use of SU together with metformin led to a 1.99 kg (95% CI: 0.86 to 3.12 kg) weight increase in two trials, while the use of TZD with metformin led to weight increase of 2.30 kg (95% CI: 1.70 to 2.90 kg) in one trial. By contrast, four trials using DPP-4 inhibitors reported a weight loss of -0.09 kg (95% CI: -0.47 to 0.30 kg), while two trials employing GLP-1 analogues obtained a weight reduction of -1.76 kg (95% CI: -2.90 to -0.62 kg). Furthermore, Kim and Chung (2014) reported considerable weight loss of 2.5 kg and 3.5 kg due to administration of canagliflozin in 100

and 300 mg concentration, respectively, during week 52 of treatment, which contrasted with the placebo. There was a big change on weight loss and cardiovascular outcomes when used empagliflozin in patients with type 2 diabetes. An earlier RCT (EMPA-REG OUTCOME trial) of 7,020 participants with type 2 diabetes and a BMI $\leq$45 kg/m^2 were randomly assigned to receive 10 mg or 25 mg of empagliflozin or a placebo once a day. All the participants had experienced CVD. After 3 years, there was a significant lower rate of death from cardiovascular causes (3.7%) in the empagliflozin group when compared with the placebo group (5.9%) and lower rate of hospitalisation for heart failure (2.7% vs. 4.1%, respectively) (Zinman *et al*., 2015).

Domecq *et al.* (2015) systematically reviewed 257 RCTs and conducted a meta-analysis to explore the correlation between commonplace medication and weight change. They found that pioglitazone and gliclazide increased weight by 2.6 kg and 1.8 kg, respectively. On the other hand, metformin, acarbose, liraglutide and exenatide reduced weight by 1.1 kg, 0.4 kg, 1.7 kg, and 1.2 kg, respectively. In the SCALE diabetes RCT (Davies *et al*., 2015) that was conducted in 9 countries, from June 2011 to January 2013, to assess the efficacy of liraglutide for weight loss among people with type 2 diabetes, 211 participants received 1.8 mg liraglutide (diabetes dose) and 212 patients received a placebo. All the patients were put on a 500 kcal/d deficit diet and $\geq$150 min/week exercise regime. At week 56, the mean weight loss in the liraglutide group and the placebo group was -5.0 kg and -2.2 kg, respectively (the estimated weight difference between the two groups was -2.8 kg).

Marre *et al.* (2009) carried out a double-blind RCT among 1,041 participants from 21 European and Asian countries, with average age and average weight of 56 years old and 82 kg, respectively. They were allocated to different groups that were given 2-4 mg/day glimepiride alongside 0.6, 1.2, or 1.8 mg of liraglutide, or else that were given placebo or rosiglitazone over a period of 26 weeks. Upon trial completion, liraglutide in 1.8 mg dose and placebo resulted in an average weight reduction of 0.2 kg and 0.1 kg, respectively (p <0.05). There was statistical significance (p <0.0001) to the difference between liraglutide (-0.2 kg) and rosiglitazone (+2.1 kg).

To sum up, on the basis of the results of the RCTs outlined above it can be concluded that some anti-diabetic drugs, such as drugs falling within the SUs and TZDs groups, might cause weight gain. Other group of drugs, such as metformin or GLP-1 and SGLT2 group drugs, might cause weight loss or not affect weight at all.

1.9 Summary of the introduction

Obesity is characterised by excessive body fat accumulation, mainly caused by increased calories intake and reduced energy expenditure. Genetic and lifestyle factors are the most important factors that play a role in the development of obesity. BMI is the most commonly used measure of obesity; it is easily measured and understood by the patient population. Obesity prevalence is rapidly increasing worldwide, in developed and developing countries. Worldwide, around 1.4 billion adults are overweight and more than 500 million are obese. 2.8 million individuals are dying annually from complications related to being overweight or obese. In Scotland, about 61.9% of the adult population are overweight or obese, and 27% are obese. Obesity is associated with increased morbidity and mortality; however, moderate weight losses (5–10%) are associated with improvements in obesity-related cardiovascular and metabolic abnormalities. There are three interventions for obesity treatment, namely, lifestyle changes and physical activity, pharmacotherapy and surgery. The SIGN guidelines recommend that weight management programmes should include physical activity, dietary change and behavioural components and the use of pharmacotherapy if BMI $\geq$28 kg/m^2 with comorbidities or BMI $\geq$30 kg/m^2. The increasing the prevalence of obesity is associated with increase in the incidence of type 2 diabetes. Orlistat is the only drug that has been approved in the UK for use in obesity treatment, and its effectiveness on both weight loss and glycaemic control has been recently proven through a number of trials. Previous studies have suggested that a modest weight loss is associated with improvements in the status of type 2 diabetes. There are different classes of anti-diabetic medications that may improve glycaemic control; weight loss, weight gain and weight maintenance were vary between the different groups.

1.10 Aims and objectives

The main evidence regarding the effect of orlistat has been compiled in the context of its application to patients without diabetes, although there have been several small to medium sized studies on the effect of orlistat in patients with type 2 diabetes. In this context, the first aim of my thesis is to review the evidence of the effect of orlistat on diabetic outcomes.

There is limited published evidence on the effectiveness of interventions in weight management programmes; the second aim of my thesis is to use large samples from the GCWMS to evaluate the effectiveness of the weight management programmes available in the UK.

There is a clear guideline (SIGN 115, 2010) for using anti-diabetic medications in patients suffering from obesity; the third aim of my thesis is to determine the anti-diabetic prescribing pattern and to investigate the relationship between anti-diabetic medications and weight change within the context of a weight management intervention.

The thesis comprises five studies that address the following specific objectives:

1. To undertake a systematic review and meta-analysis of published studies to review the evidence on the effects of orlistat on weight loss, HbA1c and FPG using the Cochrane reviews methodology.

2. To investigate the proportion of patients losing 5 kg of weight starting from entry into the GCWMS programme until the end of lifestyle phase treatment for individuals of different ages, genders and socioeconomic groups.

3. To study the proportion of patients losing 5 kg of weight starting from entry into the GCWMS programme until the end of phase 2 with three different interventions (orlistat, LDL and FWL).

4. To investigate the proportion of patients referred to the GCWMS on weight-neutral, mixed and weight-gaining anti-diabetic medications.

5. To investigate the effect of baseline anti-diabetic medications on weight change for patients within a weight management programme.

Chapter 2: Effect of orlistat on glycaemic control in overweight and obese patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials

2.1 Chapter summary

Orlistat is an effective adjunctive treatment to support lifestyle modifications to treat obesity. While the majority of current evidence concerns the effect of orlistat in obese patients without diabetes, some studies suggest patients who are obese and have diabetes mellitus lose more weight and experience greater improvements in their diabetic outcomes when treated with orlistat in conjunction with a lifestyle intervention than when treated by lifestyle interventions alone. The aim of this study was to review evidence to reveal the effects of orlistat on glycaemic control in patients who are overweight or obese with type 2 diabetes.

It comprises a systematic review of randomised controlled trials of orlistat in people with type 2 diabetes reporting diabetic outcomes, in studies published between January 1990 and September 2013. Articles published in English in MEDLINE and EMBASE were searched. Inclusion criteria included all randomised controlled trials of orlistat carried out on adult participants with a body mass index of 25 kg/m^2 or above, diagnosed with type 2 diabetes, and reporting weight change and at least one diabetic outcome.

In total, 765 articles were identified, of which 12 fulfilled the inclusion criteria. The overall mean weight reduction (3, 6 and 12 months) in the orlistat group was -4.25 kg (95% CI: -4.5 to -3.9 kg). The mean weight difference between the treatment and control groups was -2.10 kg (95% CI: -2.3 to -1.8 kg, p <0.001), the mean glycosylated haemoglobin (HbA1c) difference was -6.12 mmol/mol (95% CI: -10.3 to -1.9 mmol/mol, p <0.004), and the mean fasting plasma glucose (FPG) difference was -1.16 mmol/l (95% CI: -1.4 to -0.8 mmol/l, p <0.001).

Treatment with orlistat combined with a lifestyle intervention resulted in significantly greater weight loss and better glycaemic control in patients who are overweight or obese with type 2 diabetes, than lifestyle intervention alone.

2.2 Introduction

Estimates suggest that by 2015, approximately 2.3 billion adults will be overweight, and at least 700 million will be obese (WHO, 2014b). Obesity is causally associated with multiple metabolic abnormalities including type 2 diabetes mellitus (Birks *et al*., 2012). The World Health Organization reports that more than 347 million people worldwide suffer from diabetes, and of these most are overweight or obese. It is thought that in 2005, approximately 3.4 million people died from diabetes, and this number is predicted to double by 2030 (WHO, 2014a). Some researchers have also suggested that up to two out of every three cases of type 2 diabetes result from obesity (Davidson *et al*., 1999). Specifically, type 2 diabetes has most commonly been associated with obesity and advancing age; it is characterised by insulin resistance, relative insulin deficiency and gestational diabetes (American Diabetes Association, 2010). Thus, to improve blood glucose control, the preferred standard recommendation for care is weight loss (American Diabetes Association, 2010; SIGN 116, 2010).

Orlistat (tetrahydrolipstatin) is a pancreatic and gastric lipase inhibitor, whose primary effect is to reduce the absorption of fat and therefore calories. Long term use has been linked to reductions in blood pressure (Siebenhofer *et al*., 2013). It is one of the few pharmacologic treatment options available to assist patients with type 2 diabetes in reducing their body weight to improve glycaemic control (Yanovski and Yanovski, 2002). Orlistat works by partially inhibiting the hydrolysis of triglycerides, thereby reducing the absorption of monoglycerides and free fatty acids. Orlistat is minimally absorbed into the circulation because of its lipophilic nature. After ingestion of 360 mg of orlistat, only <2% is expelled in urine and approximately 97% in stool. The half-life of orlistat is 14-19 hrs, thus most of the drug is excreted unchanged (Zhi *et al*., 1996).

As discussed in Chapter 1 (page 56-58), the beneficial effects of orlistat on both weight loss and blood glucose have recently been proven through a number of trials. As stated above, there is evidence that orlistat in addition to lifestyle change achieves greater weight loss than lifestyle change alone (Jindal *et al*., 2012). Weight loss might also reduce the risk of developing diabetes (Stevens *et al*., 2015). While several RCTs have been carried out to describe changes in glycaemic control among patients who are obese treated with orlistat, the majority have only sampled a small number of individuals, and therefore the findings lack sufficient statistical power.

To the best of our knowledge, no previous attempts have been made to systematically review and synthesise the results of these trials.

Importantly, no serious adverse effects have been reported during orlistat treatment, and there have been no indications that it affects gastric or pancreatic secretion, or gastric emptying time. A short-term study claimed that orlistat results in several mild adverse effects on the gastrointestinal system (Kaya *et al*., 2004). These adverse effects include diarrhoea, faecal incontinence, flatulence and oily spotting. They are typically mild, with over 50% of cases lasting <1week in duration and the majority confined to the first year of treatment (80%) (Aronne, 1998). However, it is thought that orlistat might increase the chance of gallstones forming, due to the reduction in meal related contraction of gallbladder (Hopman *et al*., 1984).

The Canadian Diabetes Association clinical practice guidelines highlight that the addition of orlistat for 1 year in patients who are overweight or obese (BMI =28-40 kg/m^2) with type 2 diabetes, being treated with other anti-hyperglycaemic agents or insulin, results in a decrease in body weight and improved HbA1c (Cheng and Fantus, 2005). In addition, a European evidence-based guideline recommends that for patients who are obese with or without impaired glucose tolerance, orlistat in addition to lifestyle changes can be used as a second line strategy to prevent type 2 diabetes (Paulweber *et al*., 2010). Moreover, SIGN guidelines on the management of diabetes considered pharmacotherapy as an adjunct to lifestyle interventions, such as encouraging weight loss for patients with obesity and type 2 diabetes to improve their metabolic control (SIGN 116, 2010).

The aim of this research, therefore, was to systematically review the evidence from RCTs on the effects of orlistat in weight loss and type 2 diabetes, such as HbA1c and FPG, for people who are overweight or obese, and to combine the results using meta-analysis.

2.3 Materials and methods:

2.3.1 Systematic review

A systematic review of RCTs published between January 1990 and September 2013 was performed. The relevant search terms were applied to EMBASE and MEDLINE databases as follows:

- Obes* OR overweight OR BMI OR body mass index OR hyperphagia OR adipose tissue OR fat
- Diabet* OR diabetes mellitus OR NIDDM OR non-insulin dependent diabetes OR DM
- Orlistat OR xenical OR alli

The search was performed on 30 September 2013, and was limited to studies on human subjects and articles written in English.

Inclusion criteria

The inclusion criteria were as follows:

- Participants with BMI greater than or equal to 25 kg/m^2
- Diagnosed with type 2 diabetes
- Using orlistat at the time of the study

Studies with patients with BMIs of 25 or greater were included, on the assumption that their weight was considered a clinical problem requiring treatment with orlistat. In addition, the inclusion criteria encompassed studies with these outcomes:

- BMI or weight (kg)
- HbA1c or FPG

Participant criteria included:

- Adults ≥18 years
- Both sexes

All the completed RCTs included assessed the effects of orlistat plus lifestyle change versus a lifestyle-control group. Those reporting at least one diabetic outcome (HbA1c or FPG) were considered eligible trials. In addition, a comparison between the two groups was performed as follows:

a) Lifestyle intervention + orlistat VS Lifestyle intervention

b) Lifestyle intervention + orlistat VS Lifestyle intervention + placebo.

The extracted journal articles were all scanned using the Cochrane reviews methodology in three stages by two independent authors (having attended a systematic review and meta-analysis of health research course at London School of Hygiene and Tropical Medicine from 2nd to 6th September 2013). Any disagreements were resolved by discussion. The articles were initially identified by scanning the title and abstract; in cases where they still appeared to be relevant, then the complete article was then examined. All final decisions were derived according to a standardised approach, applying study selection criteria outlined above. The risk of bias in the trials was reduced by assessing the trial quality, including the quality of the sequence generation and random allocation concealment, the blinding of outcome assessors, evidence of incomplete outcome data and any selective reporting of outcomes (Higgins *et al*., 2008).

The Data were extracted from each study and reported according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher *et al*., 2010). A matrix table of study characteristics was produced, and from this relevant information was extracted by two independent authors. The information included author, year of publication, publication country, age and sex of participants, follow-up duration, sample size, type of intervention, baseline for outcomes, outcomes results, and the differences between the baseline and results for each group of participants. The authors of the studies were contacted in some instances where necessary to provide additional information not included in the published papers.

2.3.2 Meta-analysis

A random effects meta-analysis was undertaken to resolve of the differences in study designs and locations. The effect size of the mean weight, HbA1c and FPG differences between orlistat and the control groups was analysed. I-squared statistics were calculated to determine the degree of heterogeneity, and the association between weight change and HbA1c change examined using a simple linear regression. All the statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas).

2.4 Results

The search identified 765 potentially eligible citations, of which 453 were excluded because they were duplicates **(Figure 2-1)**. After reviewing the titles and the abstracts of the 312 articles, 35 were still considered relevant and the full articles were obtained. Of the 35 articles, 14 fulfilled the inclusion criteria. Two studies (Hollander *et al*., 1998; Derosa *et al*., 2012) did not provide necessary information required for the meta-analysis within the publications. Contact was attempted with the corresponding authors by both email and phone to retrieve this additional information, but no response was received. One of these studies (Hollander *et al*., 1998) had previously been provided for a meta-analysis for the National Institute for Health Research (NIHR) (Avenell *et al*., 2004); however, the authors of the meta-analysis no longer held the additional data [personal communication]. The final 12 trials published between 2002 and 2010 were selected **(Table 2-1)**. All the studies were RCTs; one study was only involved female participants (Kuo *et al*., 2006), but the remainder included both sexes.

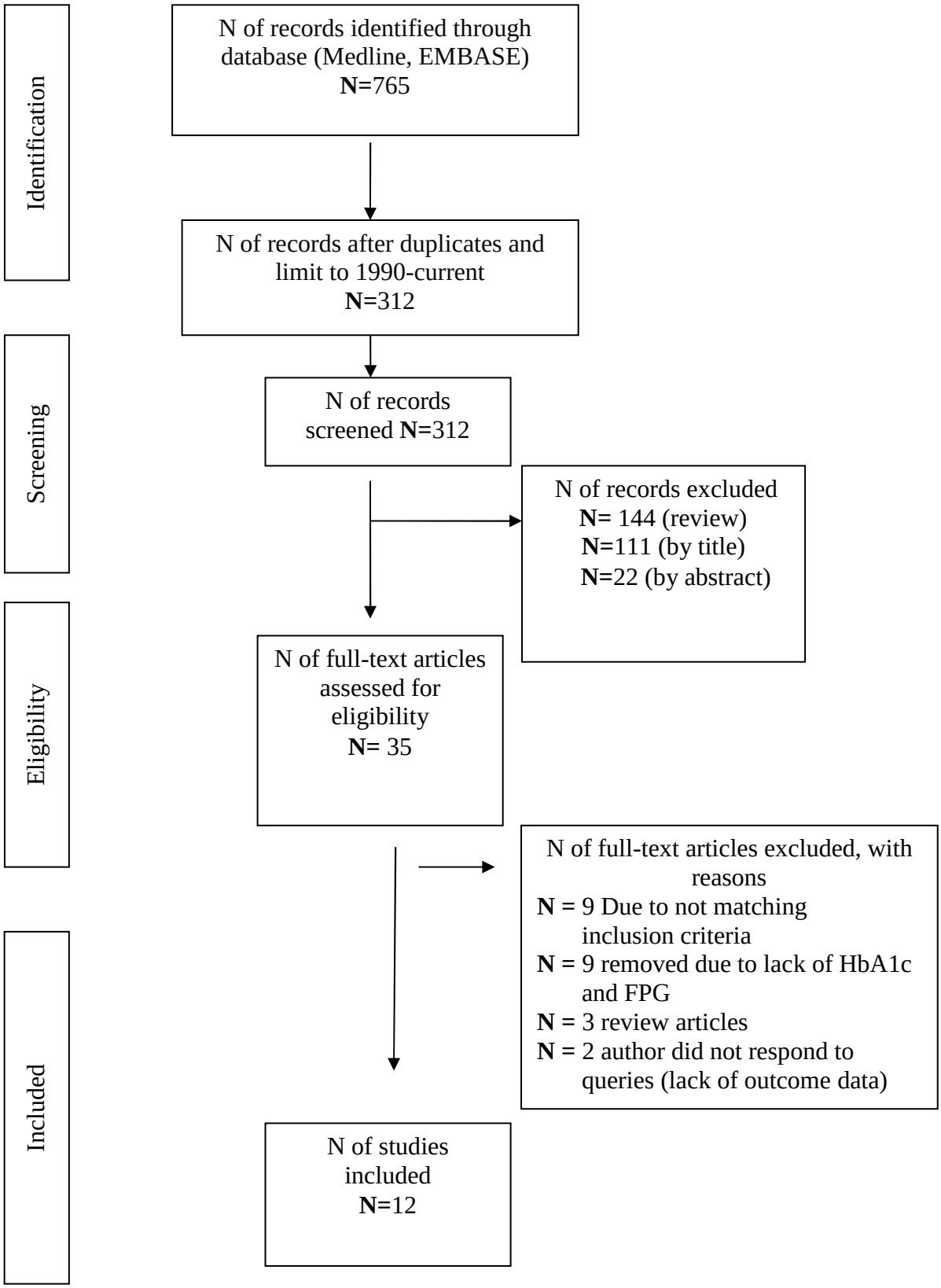

Figure 2-1 Search strategy for RCTs on glycaemic outcomes among patients with overweight and obesity treated with orlistat.

Author/ Year	Country	Age range	Sex	Duration	N	Mean BMI (SD) at baseline kg/m^2		Dropout rate (N)	
						Orlistat	Control	Orlistat	Control
P. Kopelman/2009	UK	18-65	M/F	3 months	250	35.0 (±4.1)	34.0 (±4.1)	4	7
C. Kuo/2006	Taiwan	-	F	3 months	60	27.2 (±1.1)	26.9 (±0.9)	No	No
C. Berne/2005	Sweden	30-75	M/F	12 months	220	32.6 (±3.1)	32.9 (±3.0)	15	17
T.P. Didangelos/2004	Greece	30-72	M/F	6 months	126	-	-	No	No
B. Guy-Grand/2004	France	18-65	M/F	6 months	193	33.8 (±0.3)	33.5 (±0.4)	No	No
Kelley/2004	US	-	M/F	6 months	52	34.0 (±5.0)	35.9 (±5.0)	9	4
M. Hanefeld/2002	Germany	18-70	M/F	12 months	383	34.5 (±5.6)	33.7 (±5.2)	6	8
J.M. Miles/2002	US	40-65	M/F	12 months	504	35.6 (±4.7)	35.2 (±3.1)	90	115
A. Halpern/2003	Brazil	18-70	M/F	6 months	338	34.6 (±0.8)	34.5 (±0.9)	25	33
D.E. Kelley/2002	US	40-65	M/F	12 months	550	35.8 (±4.9)	35.6 (±4.1)	137	148
G. Cocco/2005	Switzerland	≥35	M/F	6 months	90	36.5 (±1.9)	36.0 (±1.8)	No	No
M.F. Pathan/2004	Bangladesh	40-65	M/F	6 months	36	31.6 (±3.5)	29.8 (±3.2)	No	No

Table 2-1 Baseline characteristics and dropout rate of included studies (F: Female; M: Male; N: number; SD: Standard deviation).

The number of participants ranged from 36 to 550, providing a total 2,802 participants. Three (25%) of the studies had been conducted in United States (Kelley *et al*., 2004; Miles *et al*., 2002; Kelley *et al*., 2002), one (8.3%) in the United Kingdom (Kopelman *et al*., 2009), one (8.3%) in Taiwan (Kuo *et al*., 2006), one (8.3%) in Sweden (Berne and Orlistat Swedish Type 2 diabetes study, 2005), one (8.3%) in Greece (Didangelos *et al*., 2004), one (8.3%) in France (Guy-Grand *et al*., 2004), one (8.3%) in Germany (Hanefeld and Sachse, 2002), one (8.3%) in Brazil (Halpern *et al*., 2003), one (8.3%) in Switzerland (Cocco *et al*., 2005), and one (8.3%) in Bangladesh (Pathan *et al*., 2004) (Table 2-1). The youngest participants were 18 and the oldest 75 years, with multiple age ranges tested in most studies. The trials varied in duration between 3 and 12 months. Ten studies (83.3%) included participants taking hypoglycaemic agents, but two (16.6%) did not (Kelley *et al*., 2004; Hanefeld and Sachse, 2002). Details of the interventions and outcomes are apparent in **Table 2-2**.

Author/ Year	Intervention/ dose			Baseline			Results (primary end point)				Difference (primary end point)		
	a) Orlistat	b) Control	pa	Wt. (Kg)	HbA1c (%) & mmol/mol	FPG mmol/l	N	Wt. (Kg)	HbA1c (%) & mmol/mol	FPG mmol/l	Wt. (Kg)	HbA1 (%) & mmol/mol	FPG mmol/l
1) P. Kopelman/ 2009	Orlistat 360mg+hd+rf (**N=124)**	hd +rf + placebo (**N=126)**	NO	a) 101 b) 98	7.2/55 7.2/55		a) 120 b) 119	97.22 95.14	6.67/49 6.83/51		-3.78 -2.86	-0.53/-6 -0.37/-4	
2) C. Kuo/2006	Orlistat 360mg+hd (**N=30)**	hd + placebo (**N=30)**	NO	a) 76.8 b) 78.3	9.8/84 9.6/81	11.2 12.1	a) 30 b) 30	74.3 77.9	8.1/65 9.4/79	7.8 11.2	-2.5 -0.4	-1.7/-19 -0.2/-2	-3.40 -0.9
3) C. Berne/2005	Orlistat360mg+hd+rf+ pa (**N=111)**	hd +rf +pa+ placebo (**N=109**)	YES	a) 95.3 b) 95.7	7.6/60 7.6/60	11.2 10.9	a) 96 b) 92	90.54 93.98	6.5/48 7.38/56	9.3 10.64	-4.76 -1.72	-1.1/-12 -0.22/-4	-1.9 -0.26
4) T.P. Didangelos/2004	Orlistat 360mg+hd+pa (**N=94)**	hd+pa (**N=32)**	YES	a) 93.4 b) 87.3	8.0/64 7.9/63	10.0 9.7	a) 94 b) 32	87.8 83.4	6.4/46 7.1/54	7.5 9.6	-5.6 -3.9	-1.6 /-18 -0.8/-9	-2.5 -0.1
5) B. Guy-Grand/2004	Orlistat 360mg+hd+rf (**N=97)**	hd +rf + placebo **(N=96)**	NO	a) 94.3 b) 91.3	7.6/60 7.7/61	9.9 10.6	a) 97 b) 96	90.4 90.0	7.1/54 7.6/60	8.51 10.1	-3.9 -1.3	-0.54/-6 0.18/-1	-1.39 -0.50
6) Kelley/2004	Orlistat 360mg+hd+rf+pa (**N=26)**	hd +rf+pa + placebo(**N=26**)	YES	a) 99.0 b)102.0	8.13/65 7.82/62	10.87 8.77	a) 17 b) 22	87.0 92.0	6.48/46 6.85/51	6.82 6.99	-10.1 -9.4	-1.65/-19 -0.97/-11	-4.05 -1.78
7) M. Hanefeld/2002	Orlistat 360mg+hd+rf **(N=195)**	hd +rf + placebo **(N=188**)	NO	a) 99.4 b) 98.4	8.6/70 8.6/70	10.95 10.95	a) 189 b) 180	94.1 95.0	7.7/61 8.1/65	9.35 10.25	-5.3 -3.4	-1.1/-9 - 1.0/-5	-1.6 -0.7
8) J.M. Miles/2002	Orlistat 360mg+hd+rf +pa (**N=250)**	hd +rf+pa + placebo (**N=254)**	YES	a)102.1 b)101.1	8.87/73 8.79/72	11.6 11.1	a) 160 b) 139	97.4 99.3	8.12/65 8.38/67	9.6 10.4	-4.7 -1.8	-0.75/-8 -0.41/-5	-2.0 - 0.7
9) A. Halpern/2003	Orlistat 360mg+hd+rf +pa **(N=164**)	hd+rf+pa +placebo **(N=174)**	YES	a) 89.7 b) 89.5	8.37/67 8.49/68	11.05 11.50	a) 139 b) 141	84.8 86.4	7.76/61 8.27/66	10.05 11.49	-4.24 -2.58	-0.61/-6 -0.22/-2	-1.00 -0.01
10) D.E. Kelley/2002	Orlistat 360mg+hd+rf +pa **(N=274)**	hd +rf+pa+placebo (**N=276)**	YES	a) 102.0 b)101.8	9.01/75 8.99/74	10.91 11.16	a) 137 b) 128	98.11 100.53	8.39/67 8.72/72	9.28 10.08	-3.89 -1.27	-0.62/-8 -0.27/-2	-1.63 -1.08
11) G. Cocco/2005	Orlistat 360mg+hd+rf +pa **(N=45**)	hd +rf+pa+placebo (**N=45)**	YES	a) 106.99 b) 105.98	7.28/55 6.92/52	10.93 10.33	a) 45 b) 45	101.58 103.50	6.78/50 6.88/51	9.19 9.71	-5.55 -2.65	-0.5 /-5 -0.04/-1	-1.74 -0.62
12) M.F. Pathan/2004	Orlistat 360mg+hd+rf +pa **(N=21)**	hd +rf+pa (**N=15)**	YES	a) 76.9 b) 73.4	8.9/74 8.0/64	9.8 10.0	a) 21 b) 15	73.8 72.3	6.9/52 6.9/52	7.7 7.7	-3.1 -1.1	-2.00/-22 -1.1/-12	-2.1 -2.3

Table 2-2 Studies results for weight loss using orlistat and type 2 diabetes outcomes (hd: hypocaloric diet; rf: reduced fat; pa: physical activity; FPG: Fasting Plasma Glucose; Wt.: Weight; N: Number).

Ten of the twelve trials included a placebo control and two did not (Didangelos *et al*., 2004; *Pathan et al*., 2004). All of the studies included a hypocaloric diet and some continued physical activity; although no specific information regarding levels or types of physical activity was provided in four of the studies (Kuo *et al*., 2006; Hanefeld and Sachse, 2002; Kopelman *et al*., 2009; Guy-Grand *et al*., 2004). All, with the exception of two, studies included a reduced fat diet (Kuo *et al*., 2006; Didangelos *et al*., 2004). Diabetes duration was not reported in the majority of the trials, with the exception of one trial, which was restricted to those with known duration of type 2 diabetes of ≤5 years (Kelley *et al*., 2004). The mean BMI values at baseline for the trials included for the orlistat group and the control group, ranged from 27.2 to 36.5 and 26.9 to 36.0 kg/m^2, respectively (Table 2-1).

All the trials reported results in terms of weight (kg), HbA1c and FPG, with the exception of one study, in which only weight and HbA1c were provided (Kopelman *et al*., 2009) (Table 2-2). Some of the included studies reported outcomes for different durations of time, in addition to the primary end point; these were then compared in the meta-analysis. All of the included trials reported gastrointestinal side effects from orlistat, including abdominal pain, defecation urgency, diarrhoea, faecal incontinence and oily stool, except for one trial (which did not choose to report side effects) (Pathan *et al*., 2004).

2.4.1 Weight change

The trials included in this review reported weight losses for primary end points of 3, 6 and 12 months (Table 2-2). Kelley's (2004) study reported the largest weight loss for both the orlistat and placebo control groups, while Kuo (2006) and Pathan (2004) reported the smallest. There were also patterns determined by the duration of the trials. Studies of three months of duration provided the smallest weight change compared with those of six and twelve months duration. Figure 2-2 displays rapid weight loss within three months duration in both the treatment and control groups. However, the mean weight loss was higher for the treatment group (i.e. the mean weight change for the eight studies at three months duration in orlistat and control groups was -3.67 and -2.32 kg, respectively **(Figure 2-2 and Table 2-3)**. The included studies reported continued weight loss within the time in the orlistat group (i.e. the mean weight change of ten studies at six months and four studies at twelve months in the orlistat group was -4.52 and -4.63 kg, respectively). A greater overall (3, 6 and 12 months) mean weight reduction was reported when administering the orlistat treatment compared to a lifestyle intervention with or without placebo (-4.25 kg, 95% CI: -4.5 to -3.9 vs -2.27 kg, 95% CI: -2.6 to -1.8 kg, p <0.001).

Figure 2-3 and Table 2-4 depict an overall effect size in weight loss between the treatment groups and control groups of -2.10 kg (95% CI: -2.3 to -1.8, p <0.001), which indicates the difference in weight change between the treatment groups and the control groups was significantly greater with orlistat. The results were grouped into those reporting 3, 6 and 12 monthly primary end points, respectively. As expected, longer duration trials were associated with greater weight losses. The overall I-squared (test of heterogeneity) was 76.6%, p =0.001, which indicates substantial heterogeneity between the studies. There was no significant heterogeneity between the studies reporting weight change after three months (I-squared =31%, p =0.17).

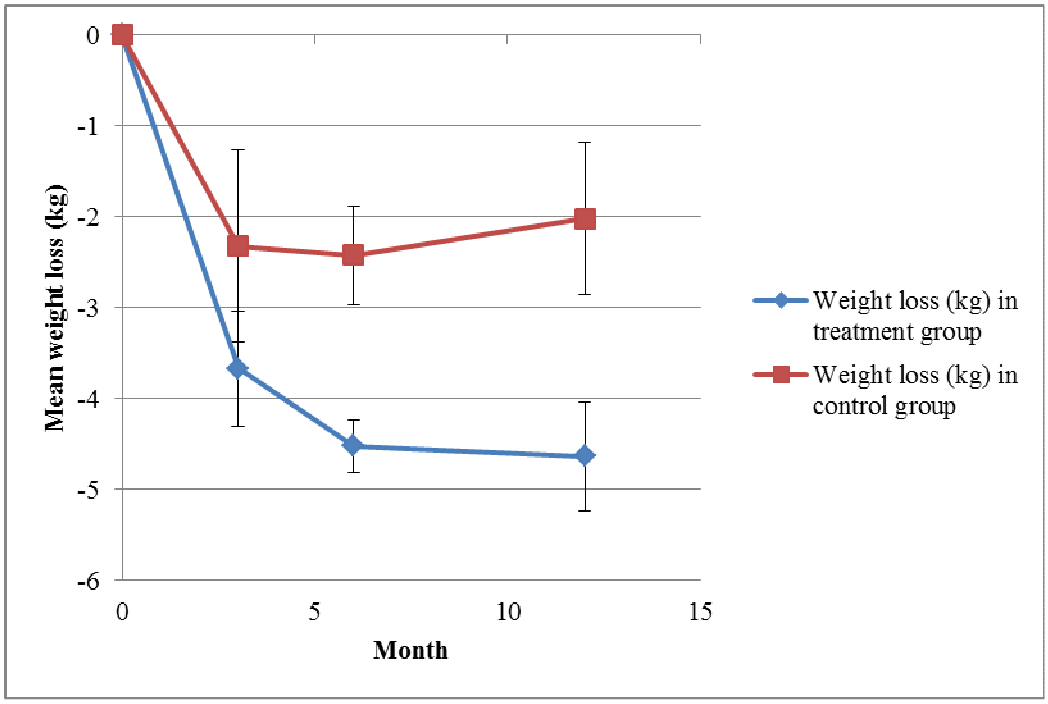

Figure 2-2 Mean weight change in all patients receiving orlistat or placebo by duration.

Duration (Months)	N. of studies	N	Orlistat				N	Control			
			Pooled estimate		Heterogeneity			Pooled estimate		Heterogeneity	
			ES (95% CI)	*P*	I^2 (%)	*P*		ES (95% CI)	*P*	I^2 (%)	*P*
3	8	1165	-3.67 (-4.30 to -3.04)	0.001	88.8	0.001	1174	-2.32 (-3.37 to -1.26)	0.001	95.7	0.001
6	10	1271	-4.52 (-4.81 to -4.23)	0.001	92.5	0.001	1207	-2.42 (-2.96 to -1.88)	0.001	95.6	0.001
12	4	824	-4.63 (-5.24 to -4.01)	0.001	71.6	0.014	819	-2.02 (-2.86 to -1.18)	0.001	85.1	0.001

Table 2-3 Pooled estimate of mean weight change (kg) by duration in orlistat and control group (ES: effect size; Cl: confidence interval; N: Number).

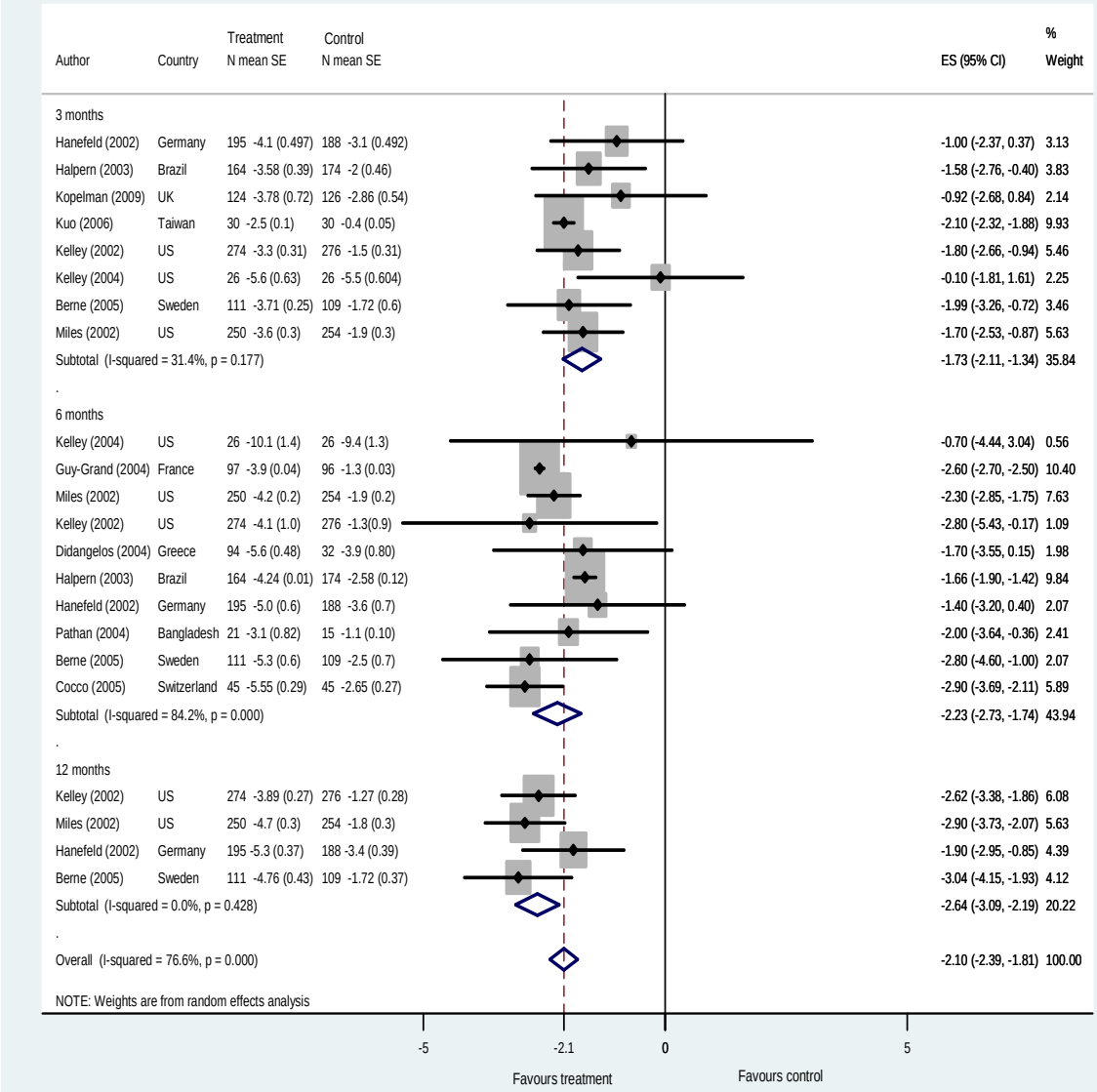

Figure 2-3 Forest plots for the weight difference (kg) between orlistat and control groups by duration (ES: Effect Size; I-squared: test of heterogeneity).

Duration (Months)	N. of studies	Difference			
		Pooled estimate		Heterogeneity	
		ES (95% CI)	*P*-value	I^2 (%)	*P*-value
3	8	-1.73 (-2.12 to -1.34)	0.001	31.1	0.17
6	10	-2.23 (-2.73 to -1.74)	0.001	84.2	0.001
12	4	-2.64 (-3.09 to -2.19)	0.001	0.0	0.42
Total difference		-2.10 (-2.39 to -1.81)	0.001	76.6	0.001

Table 2-4 Pooled estimate of mean weight difference (kg) between the orlistat and control groups (ES: effect size; Cl: confidence interval; N: Number).

2.4.2 Glycaemic values

The reduction in both HbA1c and FPG in the orlistat treatment groups was greater than in the control groups (Table 2-2).

2.4.2.1 HbA1c

Pathan (2004) reported the largest HbA1c change and Cocco (2005) the smallest. Overall mean HbA1c levels decreased more in the treatment groups than in the control groups (-11.05 mmol/mol, 95% CI: -15.0 to -7.0 vs -4.08 mmol/mol, 95% CI: -4.8 to -3.2, p <0.001), and the overall effect size difference was -6.12 mmol/mol (95% CI: -10.3 to -1.9, p <0.004). This indicates a difference in HbA1c between the treatment groups and the control groups; it was significantly greater with orlistat **(Figure 2-5 and Table 2-6)**. There was no significant difference in HbA1c changes between the treatment and control groups at 3 months (-6.46 mmol/mol [95% CI -14.06 to 1.13], p <0.095), and concerning this there was considerable heterogeneity between studies (I^2 =99.3%, p =0.001). Among studies reporting 6-monthly outcomes, the additional change in HbA1c in the treatment groups was -5.04 mmol/mol (95% CI: -5.86 to -4.21 mmol/mol). Heterogeneity remained considerable (I^2 =82.8%, p <0.001). At 12 months, the additional HbA1c change in the orlistat treatment groups was –5.29 mmol/mol (95% CI: -7.31 to -3.27 mmol/mol), again with considerable heterogeneity (I^2 =100%, p <0.001). The greatest effect from orlistat on HbA1c level occurred after 3 months duration in 5 studies -11.36 mmol/mol (95% CI: -17.53 to -5.19 mmol/mol) **(Figure 2-4 and Table 2-5)**.

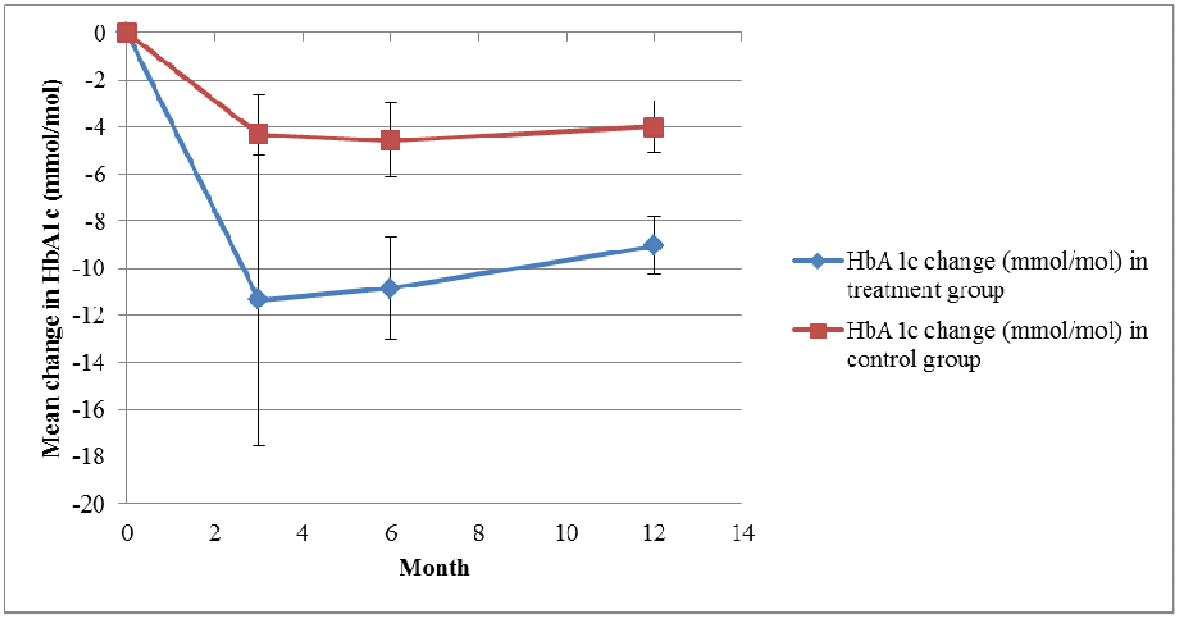

Figure 2-4 Mean HbA1c change in all patients receiving orlistat or placebo by duration.

Duration (Months)	N. of studies	Orlistat N	Orlistat Pooled estimate ES (95%CI)	Orlistat Pooled estimate *P*	Orlistat Heterogeneity I^2 (%)	Orlistat Heterogeneity *P*	Control N	Control Pooled estimate ES (95%CI)	Control Pooled estimate *P*	Control Heterogeneity I^2 (%)	Control Heterogeneity *P*
3	5	725	-11.36 (-17.53 to -5.19)	0.001	99.4	0.001	720	-4.33 (-6.02 to -2.63)	0.001	90.8	0.001
6	9	1021	-10.86 (-13.02 to -8.69)	0.001	99.3	0.001	953	-4.57 (-6.16 to -2.97)	0.001	98.7	0.001
12	4	824	-9.06 (-10.29 to -7.82)	0.001	88.4	0.001	819	-3.98 (-5.07 to -2.89)	0.001	84.9	0.001

Table 2-5 Pooled estimate of mean HbA1c (mmol/mol) change by duration in orlistat and control groups (ES: Effect size; Cl: confidence interval; N: Number).

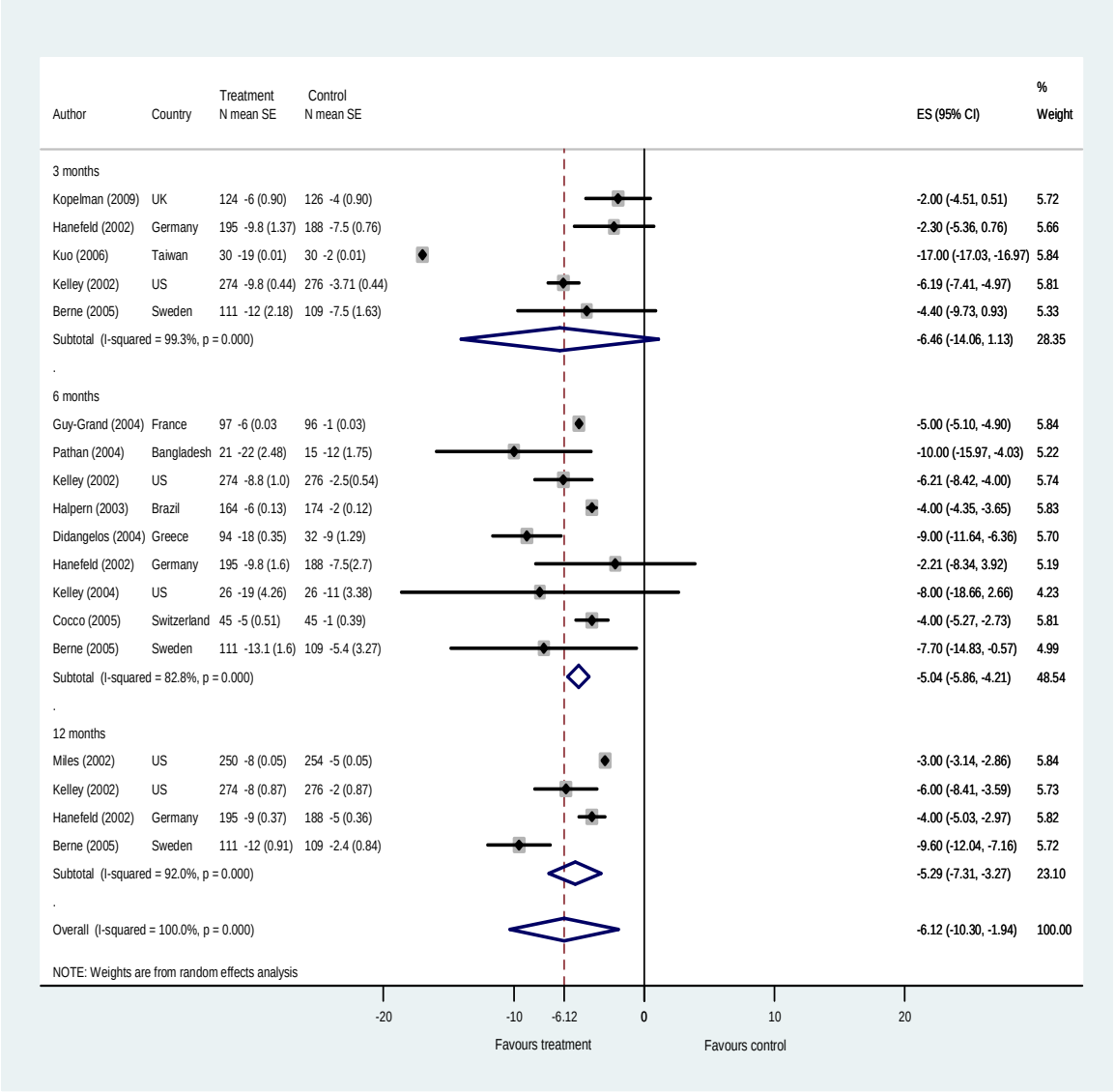

Figure 2-5 Forest plots for the HbA1c difference (mmol/mol) between the orlistat and control groups by duration (ES: Effect Size; I-squared: test of heterogeneity).

Duration (Months)	N. of studies	Difference			
		Pooled estimate		Heterogeneity	
		ES (95% CI)	*P*-value	I^2 (%)	*P*-value
3	5	-6.46 (-14.06 to 1.13)	0.09	99.3	0.001
6	9	-5.04 (-5.86 to -4.21)	0.001	82.8	0.001
12	4	-5.29 (-7.31 to -3.27)	0.001	92.0	0.001
Total difference		-6.12 (-10.30 to -1.94)	0.004	100	0.001

Table 2-6 Pooled estimate of mean HbA1c difference (mmol/mol) between the orlistat and control groups (ES: Effect size; Cl: confidence interval; N: Number).

2.4.2.2 FPG

Kelley's (2004) study reported the largest FPG change, while Halpern (2003) found the smallest FPG change (Table 2-2). The mean overall FPG levels fell more significantly in the treatment groups than in the placebo groups (-2.05 mmol/l, 95% CI: -2.3 to -1.7 vs -0.80 mmol/l, 95% CI: -1.0 to -0.5, p <0.001), and the overall effect size difference was -1.16 mmol/l (95% CI: -1.4 to -0.8, p <0.001). The FPG difference between the orlistat and control groups (-1.36 mmol/l, 95% CI: -2.59 to -0.13) over a three months duration was larger than that at the six and twelve month intervals **(Figure 2-7 and Table 2-8)**. However, there was considerable heterogeneity between the studies (I^2 =98.9%, p <0.001). Over the six and twelve month periods, the differences in FPG were -1.12 mmol/l (95% CI: -1.34 to -0.90) and -1.06 mmol/l (95% CI: -1.44 to -0.68), respectively. At 12 months, heterogeneity was low (I^2 =15.5%, p =0.31). The highest changes in FPG occurred within three months of the commencement of the trial in four studies, -2.42 mmol/l (CI: -3.43 to -1.4 mmol/l) in the treatment groups and -1.04 mmol/l (-1.26 to-0.82 mmol/l) in the control groups **(Figure 2-6 and Table 2-7)**.

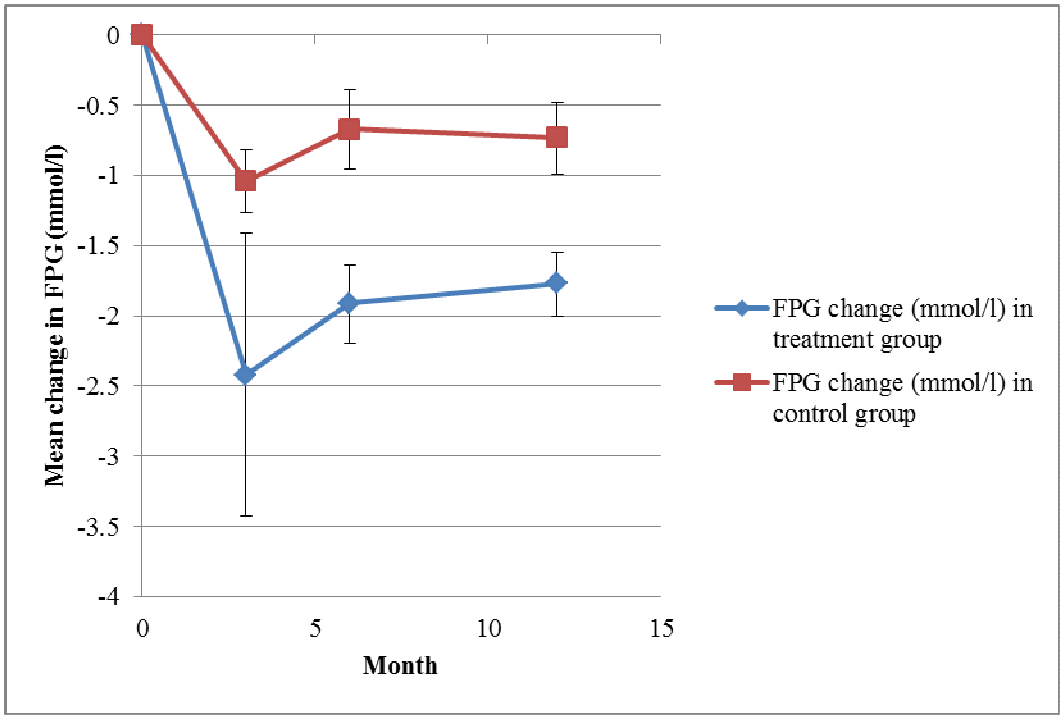

Figure 2-6 Mean FPG change in all patients receiving orlistat or placebo by duration

Duration (Months)	N. of studies	Orlistat N	Orlistat Pooled estimate ES (95%CI)	Orlistat Pooled estimate *P*	Orlistat Heterogeneity I^2 (%)	Orlistat Heterogeneity *P*	Control N	Control Pooled estimate ES (95%CI)	Control Pooled estimate *P*	Control Heterogeneity I^2 (%)	Control Heterogeneity *P*
3	4	604	-2.42 (-3.43 to -1.41)	0.001	98.9	0.001	595	-1.04 (-1.26 to -0.82)	0.001	83.2	0.001
6	10	1271	-1.91 (-2.19 to -1.64)	0.001	97.9	0.001	1207	-0.67 (-0.95 to -0.39)	0.001	97.4	0.001
12	4	824	-1.77 (-2.00 to -1.55)	0.001	0.0	0.45	824	-0.73 (-0.99 to -0.48)	0.001	0.0	0.48

Table 2-7 Pooled estimate of mean FPG (mmol/l) change by duration in the orlistat and control group (ES: effect size; Cl: confidence interval; N: Number).

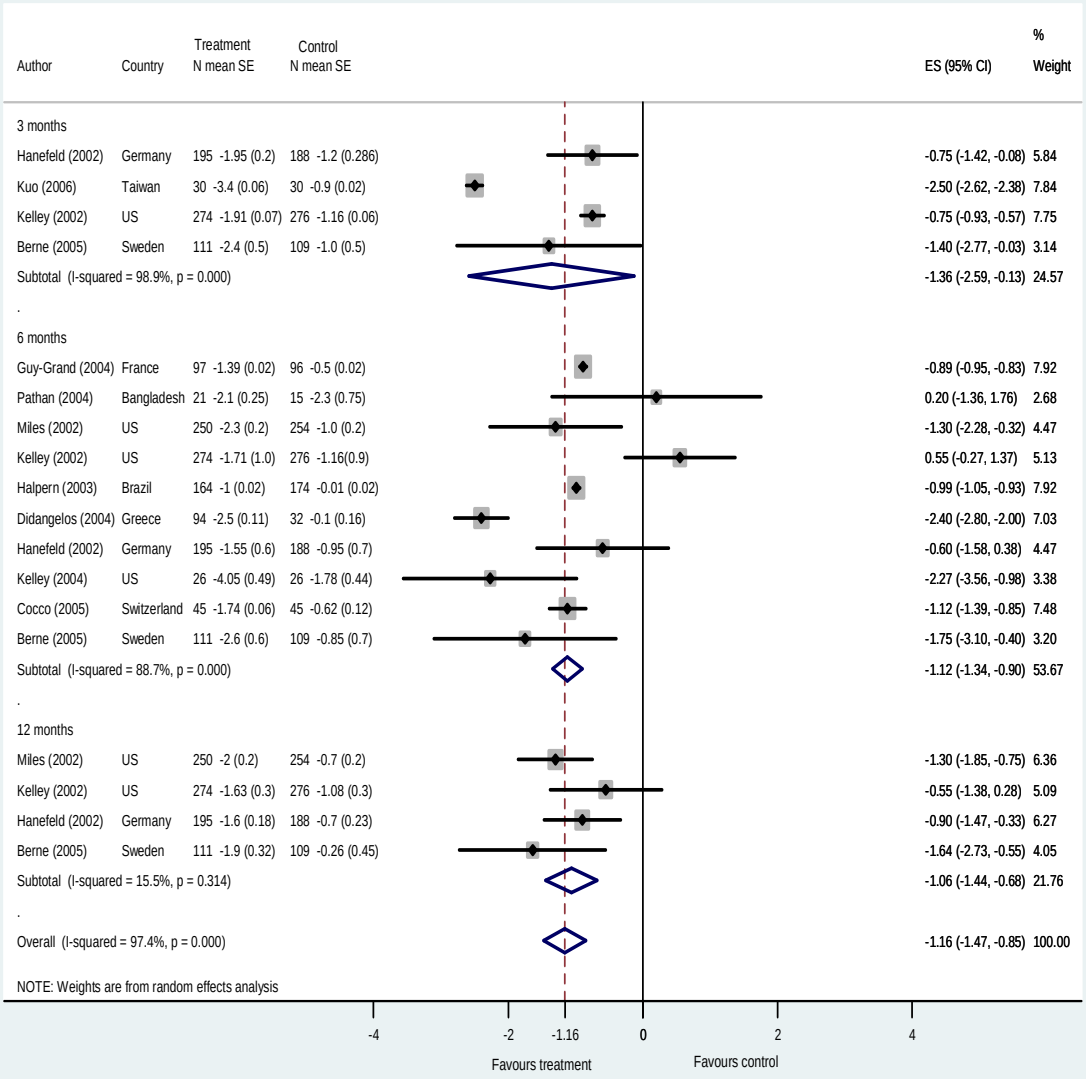

Figure 2-7 Forest plots for the FPG difference (mmol/l) between the orlistat and control groups by duration (ES: Effect Size; I-squared: test of heterogeneity).

Duration (Months)	N. of studies	Difference			
		Pooled estimate		Heterogeneity	
		ES (95% CI)	*P*-value	I^2 (%)	*P*-value
3	4	-1.36 (-2.59 to -0.13)	0.030	98.9	0.001
6	10	-1.12 (-1.34 to -0.90)	0.001	88.7	0.001
12	4	-1.06 (-1.44 to -0.68)	0.001	15.5	0.314
Total difference		-1.16 (-1.47 to -0.85)	0.001	97.4	0.001

Table 2-8 Pooled estimates for the mean FPG difference (mmol/l) between the orlistat and the control groups (ES: effect size; Cl: confidence interval; N: Number).

2.4.3 Relationship between weight and HbA1c

In order to investigate the relationship between weight differences and HbA1c differences, **Figure 2-8** shows a regression line for the weight difference and the HbA1c difference. The majority of the study points are clustered toward the lower left corner of the plot for the control groups and the upper middle for the treatment group. There are four outlier studies, which lie away from the main data cluster, denoting where HbA1c reduction is far greater than that expected for the weight loss reported (Kuo *et al*., 2006; Kelley *et al*., 2004; Didangelos *et al*., 2004; Pathan *et al*., 2004). The adjusted R^2 is 19.3%, indicating 19.3% of the variability in the HbA1c difference can be explained by its dependence on weight difference. The estimated coefficient for the treatment and control groups is -1.25, which tells us the average HbA1c decreases by 1.25 mmol/mol for every 1 kg drop in weight **(Table 2-9)**.

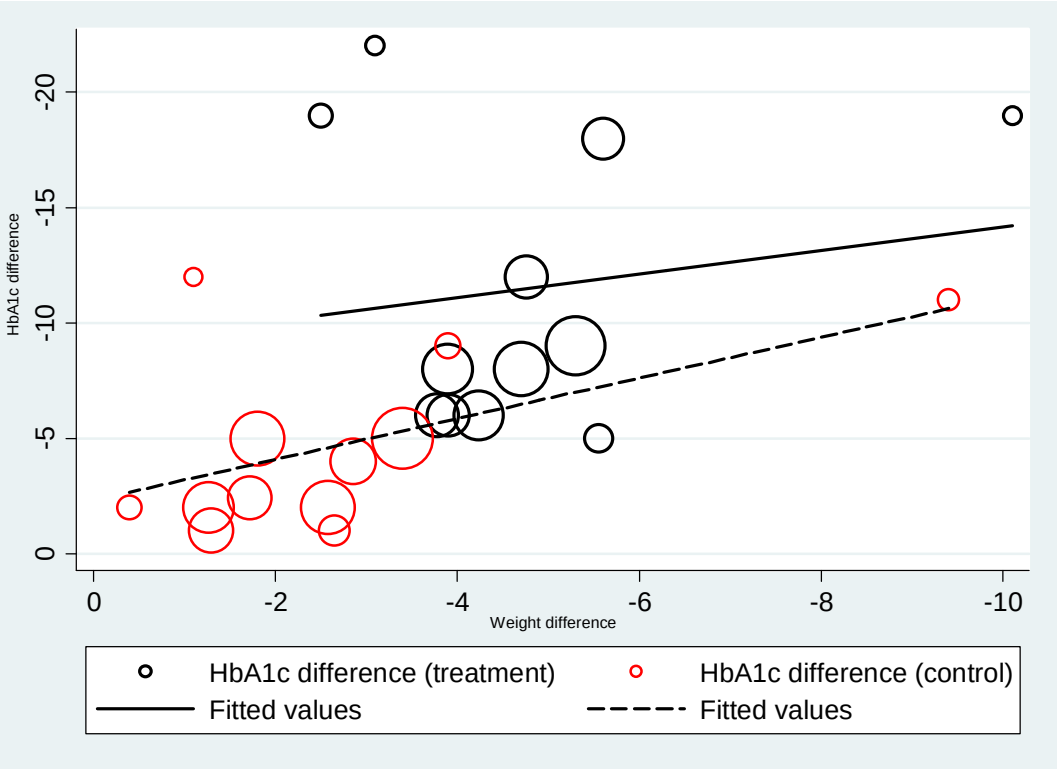

Figure 2-8 Simple linear regression between HbA1c difference and weight difference at the primary end point (The circle sizes represent the sample sizes).

HbA1c difference	**Coefficient mmol/mol**	**Standard error**	***P*-value**	**Confidence interval**	**R-squared**	**Adjusted R-squared**
Weight difference	1.25	0.49	0.018	0.23 to 2.26	0.229	0.193

Table 2-9 Weight difference and HbA1c difference regression model for the treatment and control groups.

2.4.4 Effects of physical activity and placebo

The effects of physical activity and placebo were also considered, and are as shown in **Table 2-10**. There was no significant difference apparent in the weight differences between those studies that included physical activity and those that did not, at any of the time points. The effect of the placebo on weight change could only be evaluated at 6 months, and at this point no significant effect was found. Physical activity apparently had no effect on HbA1c at any of the time points. The addition of a placebo was associated with a significant difference in HbA1c at 6 months, only. FPG effects were not influenced by either physical activity or the use of a placebo at any time point.

	3 months			6 months			12 months			Total *P*-value (PA)
Weight (PA) Kg	N. of study	Results (difference between treatment and control)	*P*-value	N. of study	Results (difference between treatment and control)	*p*-value	N. of study	Results (difference between Treatment and control)	*p*-value	
Yes	5	-1.4	0.501	8	-2.1	0.618	3	-2.8	0.267	
No	3	-1.3		2	-2.0		1	-1.9		
Placebo										
Yes	8	-1.4		8	-2.1	0.588	4	-2.6		0.686
No	0	0		2	-1.8		0	0		
HbA1c (PA) mmol/mol										
Yes	2	-5.2	0.796	7	-6.9	0.432	3	-6.2	0.643	
No	3	-7.1		2	-3.6		1	-4.0		0.837
Placebo										
Yes	5	-6.3		7	-5.3	0.012	4	-5.6		
No	0	0		2	-9.5		0	0		
FPG (PA) mmol/l										
Yes	2	-1.07	0.567	8	-1.1	0.603	3	-1.1	0.683	
No	2	-1.62		2	-0.7		1	-0.9		0.899
Placebo										
Yes	4	-1.3		8	-1.0	0.513	4	-1.0		
No	0	0		2	-1.1		0	0		

Table 2-10 Effects of physical activity and placebo on weight loss, HbA1c and FPG (PA: Physical activity; N: Number).

2.5 Assessment of bias

The risk of bias was assessed using guidelines provided by the Cochrane Collaboration (Higgins & Green, 2008), and as set out in **Table 2-11**. Generally, bias was found to be low in all the included studies, as shown in **Table 2-12**. However, allocation concealment and blinding of participants and personnel were not reported in Didangelos' (2004) study; sequence generation was unclear, nor was it apparent which were the primary and secondary outcomes intended in Cocco's (2005) study; and the blinding of participants and personnel was not reported by Pathan (2004). All the studies reported the blinding of outcome assessment, and none reported missing data.

Type of bias	Description	Relevant domains in the Risk of Bias tool
Selection bias	Systematic differences between the baseline characteristics of the groups	• Sequence generation • Allocation concealment
Performance bias	Systematic differences between the groups in the care that is provided, or in exposure to factors other than the interventions of interest	• Blinding of participants and personnel • Other sources of bias
Detection bias	Systematic differences between groups in how outcomes are determined	• Blinding of outcome assessment. • Other sources of bias
Attrition bias	Systematic differences between groups in withdrawals from a study	• Incomplete outcome data
Reporting bias	Systematic differences between reported and unreported findings	• Selective outcome reporting

Table 2-11 Classification scheme used to assess bias (Cochrane Handbook).

RCT	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	No (%) of criteria in each study (*n*=6)
P. Kopelman/2009	Y	Y	Y	Y	Y	Y	6 (100)
C. Kuo/2006	Y	Y	Y	Y	Y	Y	6 (100)
C. Berne/2005	Y	Y	Y	Y	Y	Y	6 (100)
T.P. Didangelos /2004	Y	N	N	Y	Y	Y	4 (66.6)
B. Guy Grand/2004	Y	Y	Y	Y	Y	Y	6 (100)
Kelley/2004	Y	Y	Y	Y	Y	Y	6 (100)
M. Hanefeld/2002	Y	Y	Y	Y	Y	Y	6 (100)
J.M. Miles/2002	Y	Y	Y	Y	Y	Y	6 (100)
A. Halpern/2003	Y	Y	Y	Y	Y	Y	6 (100)
D.E. Kelley/2002	Y	Y	Y	Y	Y	Y	6 (100)
G. Cocco/2005	UNCLEAR	Y	Y	Y	Y	N	4 (66.6)
M.F. Pathan/2004	Y	Y	N	Y	Y	Y	5 (83.3)
No. (%) of studies containing criterion (*n*=12)	11 (91.6)	11 (91.6)	10 (83.3)	12 (100)	12 (100)	11 (91.6)	

Table 2-12 Study design criteria aimed at reducing bias: Abbreviations: Y, the criterion was present (low risk of bias); N, the criterion was not present (high risk of bias); UNCLEAR (uncertain risk of bias).

2.6 Summary of the main findings

- Greater reduction in weight, HbA1c and FPG in the orlistat treatment groups compared with the control groups.
- The reductions in HbA1c and FPG in the treatment group occurred quickly in the first 3 months.
- With orlistat treatment, longer duration studies were associated with greater weight loss when compared with shorter duration trials.
- There was no significant effect of adding physical activity to the overall outcomes.
- There was a significant effect of the absence of a placebo on HbA1c differences between orlistat and control group at 6 months duration.

2.7 Discussion

The initial systematic review and meta-analysis of the RCTs was conducted to describe the effects of orlistat on glycaemic control among patients with overweight and obesity. It was found that the addition of orlistat to lifestyle changes increased weight loss, and was associated with greater reductions in both HbA1c and FPG levels that were clinically significant. The addition of physical activity to the regimen did not significantly affect overall weight loss or glycaemic control. There was also little evidence that the use of a placebo influenced the observed results.

A previous systematic review by Avenell *et al*. (2004) reported a weight reduction in the first year across eight RCTs including patients both with and without diabetes. Only one of these studies met the criteria for the review (Hollander *et al*., 1998); however, the published data were not sufficient for inclusion as further information would have been required but was not available from either the author of the study or the authors of the systematic review. The mean weight difference between the orlistat plus diet group and the placebo plus diet groups after 12 months was -3.01 kg (95% CI: -3.48 to -2.54 kg, p <0.00001). Of eight RCTs, six RCTs reported a FPG outcome and three reported a difference in HbA1c (both in patients with and without diabetes). The mean HbA1c change difference was -1.85 mmol/mol (95% CI: -2.62 to -1.09 mmol/mol, p <0.00001), and the mean FPG difference was -0.24 mmol/l (95% CI: -0.34 to -0.14 mmol/l, p <0.00001). Both the HbA1c and FPG reductions in Avenell's study were smaller than the research results, and this is probably because the non-diabetic patients included in Avenell's analysis had lesser capacity for glycaemic improvements, despite greater weight losses.

All the results in the studies included in this systematic review and meta-analysis showed a reduction in weight and glycaemic values in the orlistat and control groups, although the mean reduction within the time frame in the orlistat group was greater than in the control groups. The reduction of weight, HbA1c and FPG was clinically and statistically significant after using orlistat. The reductions in HbA1c and FPG in the orlistat group occurred in the first 3 months. They were followed by modest rises thereafter, despite continued weight losses of up to 12 months. It might be that, as adherence to lifestyles reduces over time, glycaemic control deteriorates. Miles *et al*. (2002) found that, when patients were treated with orlistat 120 mg, an improvement in glycaemic control occurred quickly with the onset of caloric restriction, prior to any weight loss. Additionally, Rowe *et al*. (2005) showed that, 6 months of orlistat treatment in patients with obesity and diabetes

(receiving insulin) was associated with significant reduction in the mean dose of insulin without any correlation with weight loss being observed.

Outlier studies were identified as those where the results were at a distance from the main data cluster, for unclear reasons, although in some cases these might be a consequence of the small sample size used in the studies, or because they recruited different patient populations with diabetes durations of ≤5 years (Kelley *et al*., 2004). Two studies (Kuo *et al*., 2006; Pathan *et al*., 2004) were of Asian populations, and there were several potential reasons reported, resulting in a greater effect size when using orlistat. Asian populations develop type 2 diabetes at lower BMIs (22 kg/m^2 versus 30 kg/m^2 in white Europeans), because of the capacity reductions for storing fat in the primary superficial subcutaneous adipose tissue compartment (Sattar and Gill, 2014), which might mean that less absolute weight loss was required to improve insulin sensitivity. In addition, differences in the dietary needs of the Asian population might help with orlistat's action to reduce blood glucose levels.

In this review, the effects of physical activity and the placebo on weight loss, HbA1c and FPG were unclear, due to insufficient numbers of studies reporting effects without physical activity, especially over 6 to 12 months durations. Similarly, a low number of studies reported outcomes in the absence of placebo; although, at 6 months duration there was a significant effect from the absence of placebo on HbA1c difference (i.e. the mean HbA1c difference in the presence and absence of placebo in 6 months duration was -5.3 and -9.5, p =0.012, respectively). The reason for this might be that patients in the control group effectively remembered to take their anti-diabetic medications with the placebo, or were not disheartened when blinded to their intervention. Consequently, more studies need to be undertaken to confirm the effects of physical activity and placebo on weight loss and glycaemic values.

2.8 Research Strengths and limitations

This systematic review and meta-analysis was conducted on the basis of the Cochrane reviews methodology, and was reported based on PRISMA guidelines. Two major databases were used to identify relevant trials. The pooled estimates were derived from twelve trials comprising 2,802 participants in total. Previous studies of orlistat included obese patients with and without diabetes; this research is the first systematic review to focus solely on patients with diabetes excluding others, and the effect of orlistat on glycaemic control. The strengths of this review were the inclusion of RCTs, the assessment of two types of intervention and the generation of meta-analysis.

The limitations of the review are the insufficient sample sizes in some studies and the potential to overestimate the long-term effects of treatment based on inferences from short term interventions (<6 months). In addition, treatment strategies were mixed between dietary management and a variety of oral hypoglycaemic agents. There was considerable heterogeneity between the studies identified. This remained after the results were stratified by length of trial and was found in the meta-analysis of weight, HbA1c and FPG. There are a number of ways in which the patients, the interventions and the evaluation of the intervention's effects might vary between studies. There were differences in the ages of the patients and in the mean baseline weights. Dietary habits, physical environments that might promote or inhibit physical activity and seasonal variations in weight, might also influence the effectiveness of weight loss interventions.

The presence of other comorbidities, such as heart failure, which might affect capacity for physical activity and use of medications that might promote weight gain, may also vary between the patients in different studies. Details of advice given about physical activity, and regarding whether the advice was followed were lacking. Orlistat 60 mg has been available as an over-the-counter medication in the US since 2007, and in the EU since 2009, but as this review only included studies using a prescription-only dose of 120mg, we cannot say whether the use of a 60mg dose by patients with obesity and diabetes improves glycaemic control, and further research is needed to describe these patients.

2.9 Research Implications

As observed above, the findings of all the included studies show that treatment with orlistat combined with lifestyle interventions provides benefits for individuals who are overweight or obese with type 2 diabetes. It therefore follows that orlistat should be considered an effective adjunctive treatment to lifestyle intervention and anti-diabetic medications to improve glycaemic control among patients who are overweight or obese with type 2 diabetes. However, further research is needed to confirm the effect of orlistat in real life; this is investigated in Chapter 4. Future research into the effects of orlistat on glycaemic control in overweight and obese patients with type 2 diabetes would be improved by the provision of additional detail concerning physical activity interventions, and objective monitoring of physical activity (e.g. by using an accelerometer). In addition, giving full details of the behaviour change techniques used would allow the coding of interventions within a systematic review, which would further help to build cumulative knowledge of which interventions are effective (Michie *et al*., 2013; Presseau *et al*., 2015). Recordings of comorbidities and medications and longer follow-up periods beyond 12 months are suggested. Further research is needed to measure the adherence to orlistat, as it is generally believed that people do not adhere to orlistat treatment.

Chapter 3: Evaluation of the effectiveness of phase 1 (lifestyle) of the Glasgow and Clyde Weight Management Service programme

3.1 Chapter summary

There is a paucity of evidence regarding the effectiveness of weight management services. The aim of the data collected for this chapter was to evaluate the effectiveness of the lifestyle intervention component of the NHS Glasgow and Clyde Weight Management Service (GCWMS), particularly to achieve ≥5 kg weight loss, exploring the effects of age, sex, initial weight, BMI, and co-morbidities such as diabetes and hypertension. In this prospective cohort study, all the individuals who started GCWMS between 2008 and 2014 were included. Last observation carried forward (LOCF), and programme completers were reported using mean weight changes with 95% confidence intervals, and 5 kg and 5% weight losses at the end of the lifestyle programme were observed.

Of 23,650 patients referred to GCWMS, 13,255 (56.0%) attended assessment, 8,173 (61.5%) individuals attended their first session and 7,329 (55.3%) individuals attended at least two sessions of the lifestyle programme. At the first visit, 72.9% were female, 40.5% were from the most deprived quintile, 21.4% had diabetes, 16.2% had hypertension, mean weights and BMI were 115.2 kg and 42.2 kg/m^2 respectively. In total, 30.5% of those who opted in and attended ≥2 sessions (7,329) lost ≥5 kg by the end of the lifestyle programme, and among 4,042 completers, 46% (*n* =1,854) lost ≥5 kg. Weight loss (≥5 kg) occurred at a higher rate among men, aged ≥40 years, BMI ≥50 kg/m^2. Those with diabetes mellitus, young men, young women, and socio-economically deprived groups achieved lesser weight loss.

The weight management programme was effective for achieving 5 kg weight loss, but only in less than 50% of those patients who completed a lifestyle programme. Those who did not complete the programme (44.8% dropped out) experienced a lack of weight loss. A higher proportion of the patients completing the programme lost ≥5 kg. Therefore, it is necessary to evolve the GCWMS in order to facilitate an improved impact.

3.2 Introduction

The prevalence of obesity is becoming more extensive in the UK, where it is becoming a major cause of serious diseases, including cancers and coronary artery disease (Kopelman, 2007). Treatment guidelines developed in the UK recommend multicomponent weight management programmes which include calorie deficient diets, regular physical activity (225-300 minutes/week) and behavioural components such as motivational interviewing for the management of patients with overweight or obesity (SIGN 115, 2010). The NHS Greater Glasgow and Clyde area of Scotland has a population of 1.2 million individuals. GCWMS is among the biggest services in the UK. The service is provided by a team comprising dietitians, psychologists, physiotherapists and administrative staff. GCWMS is accessible to patients aged 18 years and over with complex obesity (defined as BMI of ≥30 kg/m^2 with obesity-related comorbidities, or BMIs of ≥35 kg/m^2), who have been referred by a GP or hospital doctor.

The goal of the service is to support patients to achieve weight losses of at least 5 kg. This is based on good evidence that a 5 kg weight loss is a clinically significant target known to improve obesity associated health conditions (Robertson *et al*., 2014). GCWMS is only successful if participants are motivated to change their lifestyles, and all of the eligible patients are referred by their health professionals and they receive a leaflet about the service. Once a referral has been sent by the GP, patients have to phone the GCWMS booking centre within two weeks to arrange an assessment appointment. The assessment includes questions about the patient's weight and diet history, their levels of activity, physical health and moods and motivations. Furthermore, patients might undergo further assessment from a physiotherapist or a clinical psychologist to direct them toward the best treatment. GCWMS offers small group and individual programmes to individuals suffering from anxiety, mild learning difficulties, sensory impairment and literacy issues.

GCWMS is offered in three phases: the treatment in phase 1 (lifestyle intervention) includes a combination of diet (600 kcal deficit diet), exercise and behavioural interventions over nine sessions (90 min) delivered once every two weeks over a 16-week period (9 fortnightly sessions). Behavioural interventions include patient monitoring, motivational enhancement, and cognitive behavioural therapy such as goal setting, problem solving, and slowing the rate of eating. These sessions involve dietician talks, encouraging healthy eating based on the Eatwell Plate (Food Standards Agency, 2007) and behavioural change, in addition to weekly exercise sessions and psychological talks (full details of the

sessions can be seen in **Figure 3-1**). After completing phase 1, patients can choose to enter phase 2, which consists of four sessions (one hour) delivered at monthly intervals, and including a variety of treatment options including further lifestyle advice (FWL), a prescribed low-calorie diet (LCD) or pharmacotherapy (orlistat). Phase 2 treatments are determined by patient choice; generally, if patients successfully lose ≥5 kg, they can move on to FWL by attending three monthly sessions over 3 months, and if they have lost less than 5 kg, they will be selected for a LCD, or pharmacotherapy. Patients can then enter a weight maintenance programme (phase 3) directly following the end of the lifestyle phase, or at the end of phase 2, dependent on the patient's choice.

Phase 3 consists of 12 sessions (one hour) delivered at monthly intervals. The patient can choose to repeat phase 2 once again and then enter a maintenance programme if they fail to achieve their target weight loss (5 kg). In addition, patients can opt for bariatric surgery if they fail to lose 5 kg and have a BMI >40 kg/m^2, or BMI >35 kg/m^2 with comorbidities **(Figure 3-2)**.

There is a lack of evidence evaluating multidisciplinary tier 3 weight management programmes available in the UK. Therefore, the aim of this research was to evaluate the effectiveness of the lifestyle intervention offered by the GCWMS programme to achieve 5 kg or more weight loss, exploring the effects of age, sex, initial weight and BMI, as well as co-morbidities such as diabetes and hypertension. The main research question posed was: what proportion of patients lose 5 kg of weight during the lifestyle phase of the GCWMS?

GCWMS programme: the lifestyle phase

Session 1: General talk

- Programme overview;
- Causes of obesity;
- Benefits of 5-10 kg weight loss;
- Eat Well Plate;
- Becoming more active;
- Lifestyle diaries.

Session 2: Taking control

- PDP;
- Barriers and benefits to becoming more active.

Session 3: Planning for success

- Menu planning, shopping, and guide to food labelling;
- Binge eating.

Session 4: Changing habits

- Cooking and eating out/takeaways;
- Dealing with social pressure to eat;
- What you can do to incorporate physical activity.

Session 5: Go do it

- Solve unhelpful thinking - thoughts, feelings, and behaviour;
- Diet quiz.

Session 6: Riding the craving wave

- Cravings vs. hunger;
- Practical dietary tips;
- Physical activity quiz.

Session 7: Keep it real

- Diet myths/fad diets, and the balance of good health;
- Staying motivated to be active;
- Body image.

Session 8: The journey so far

- Relapse prevention;
- Support;
- High risk situations;
- What activity changes have been made?

Session 9: Programme review and phase 2 offering

Figure 3-1 Patients' journey at the lifestyle phase.

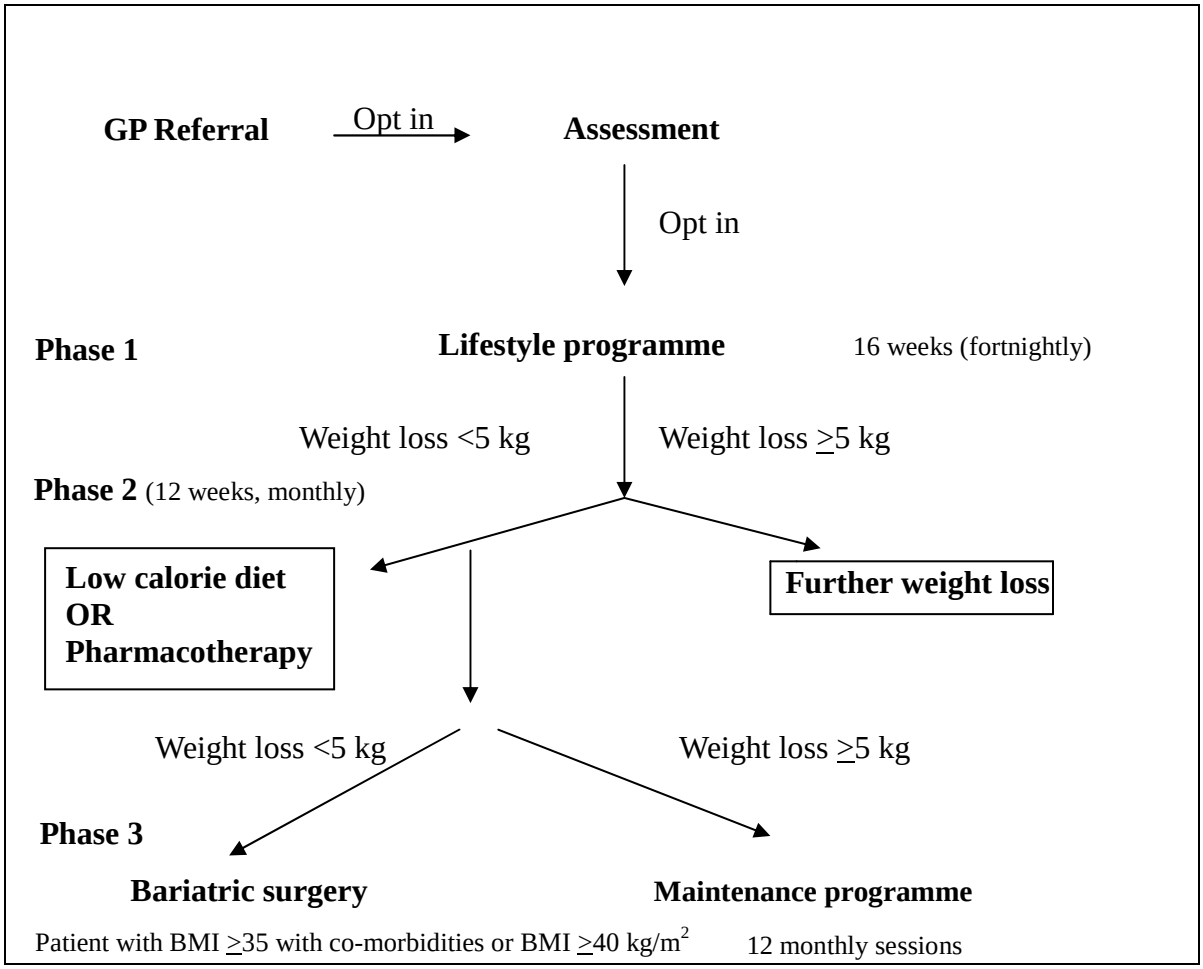

Figure 3-2 Diagram of the phases of the Glasgow and Clyde Weight Management Service.

3.3 Materials and methods

3.3.1 Data source

The data were collected by the dietitians at the time when the participants attended their sessions at the GCWMS. The subjects' weight and height were measured by the dietitians on calibrated scales, and then noted. These data were then recorded and transferred to a database by the dietitians. This prospective cohort study used data obtained for all referrals made to the GCWMS from 2008 to 2014. The data were collected on a live database and stored on a Microsoft Structured Query Language (SQL) server. The data analyst at GCWMS extracted the data by running a SQL query for each table including all of the requested fields. The output from each of the SQL queries was transferred to a comma-delimited text file and then transferred to the data development manager. After this, the text files were imported into an access database.

3.3.2 Inclusion and exclusion criteria

Of the 23,650 patients identified, 13,255 opted into the service for assessment (by phoning the service after referral and making an appointment). Of these, 8,226 patients opted into the lifestyle programme, and the final number of patients attending the first session was 8,173 patients. Of these 8,173 patients, 7,329 individuals attended at least two sessions in the lifestyle phase and were included in the analysis **(Figure 3-3)**. Therefore, because the weight would not change if the individuals attended only one session, only those patients attending at least two sessions with weights recorded were included in the baseline characteristics and weight change outcomes (n =7,329).

Since human error is always possible, the data were checked and cleaned by the author. Records with ages below zero, a height of 1m or less, and a weight of less than 30 kg were excluded, as they were unlikely to produce valid data. Individuals aged less than 18 years and with a BMI below 30 kg/m^2 were excluded, because the programme is for adults with BMI $\geq$35 kg/m^2 or 30 to 34.9 kg/m^2 with co-morbidities, and therefore the data are unlikely to be valid. Therefore, 53 patients were excluded because of their age (below 18 years) and BMI (less than 30 kg/m^2). If the same patient was referred more than once, information from the earliest referral only was included (Morrison *et al*., 2011; Dixon *et al*., 2012), and the same referral was used in phase 2.

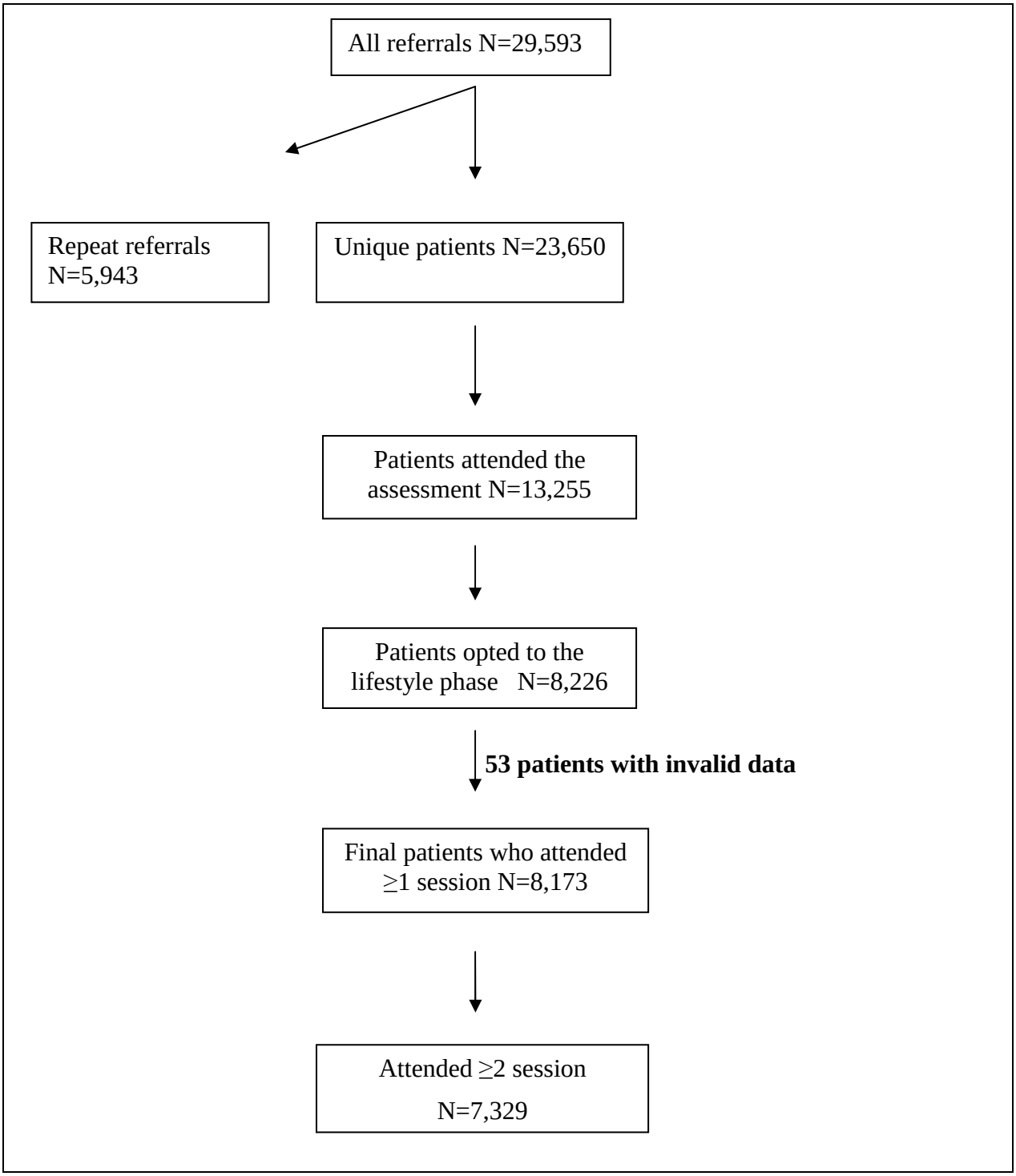

Figure 3-3 Flowchart showing all the referrals to the GCWMS between 2008 and 2014.

3.3.3 Definition of programme completion

It has been established that attendance is directly related to weight loss; therefore, programme completion was defined prior to analysis as completion of the programme with attendance at 80% of the sessions; i.e. seven or more sessions attended during the lifestyle phase. Those who completed six or fewer sessions were labelled non-completers.

3.3.4 Variables definitions

Co-morbidity information regarding the presence or absence of diabetes mellitus and hypertension were obtained using data from the GP referral form. The patients were classified as having diabetes and hypertension if either was noted on their GP referral form or mentioned by the patients at assessment. However, as social, educational and economic information were not available for the patients, we estimated socioeconomic status using the Scottish Index of Multiple Deprivation (SIMD). Scotland is divided into 6,505 datazones by postcode of residence; each contains around 350 households and has a mean population of 800 people. The SIMD for each datazone is constructed using information pertaining to seven domains: income and benefits, employment, health, education (including skills and training), housing, crime, and access to services. The SIMD is used to derive quintiles of socioeconomic status for the Scottish population; ranges from 1 (most deprived) to 5 (least deprived).

Finally, age was categorised into six groups: 18-29, 30-39, 40-49, 50-59, 60-69 and ≥70 years. BMI was categorised into four groups: (30-34.9 kg/m^2), (35-39.9 kg/m^2), (40-49.9 kg/m^2) and (≥50 kg/m^2). Weight was categorised into five groups: (<75 kg), (75-99 kg), (100-124 kg), (125-149 kg) and (≥150 kg).

3.3.5 Statistical analysis and weight loss outcomes

Missing data relating to weight are very common where a patient has left a programme early or not attended an appointment. Where data are missing, the method of LOCF was used. In other words, when the weight measurement is missing, it is replaced by the participant's last observed value. The characteristics of patients at referral, assessment and the first session were reported. However, patient's weights at the first session were also used as a baseline for this research. Mean weight change and 95% CI, 5 kg and 5% weight loss were reported. Differences in the means between the two groups and more than two

groups were tested using a t-test and ANOVA test, respectively. A stratified analysis was used to estimate the effects of potential confounding factors on weight change. These factors were sex, age, deprivation, initial weight/BMI, and presence of diabetes/or hypertension. All the statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas).

3.4 Results

3.4.1 Referral number by GP practice code

In order to investigate whether there was any variation in GPs referral rates for patients to the weight management programme, the number and percentage of referrals by GPs to the GCWMS were identified. Over a six-year duration, from 2008 to 2014, around 386 GP practices made 29,593 referrals. **Table 3-1** shows that 107 GP practices had fewer than 10 referrals in total within a six-year period. This equates to 27.7% of GPs making <10 referrals. On the other hand, 69 practices made between 100-250 referrals, and just five GP practices made more than 250 referrals. The bar chart represents the variation between the numbers of referrals by different GP practices. The majority of these practices had 100 referrals or fewer, and some had very low referred numbers to GCWMS **(Figure 3-4)**.

Referral number categories	Number of practices	%
<10	107	27.7
10- <50	87	22.5
50- <100	118	30.5
100- 250	69	17.8
>250	5	1.3

Table 3-1 Number of referred patients to the GCWMS from 2008-2014 by GP practices code.

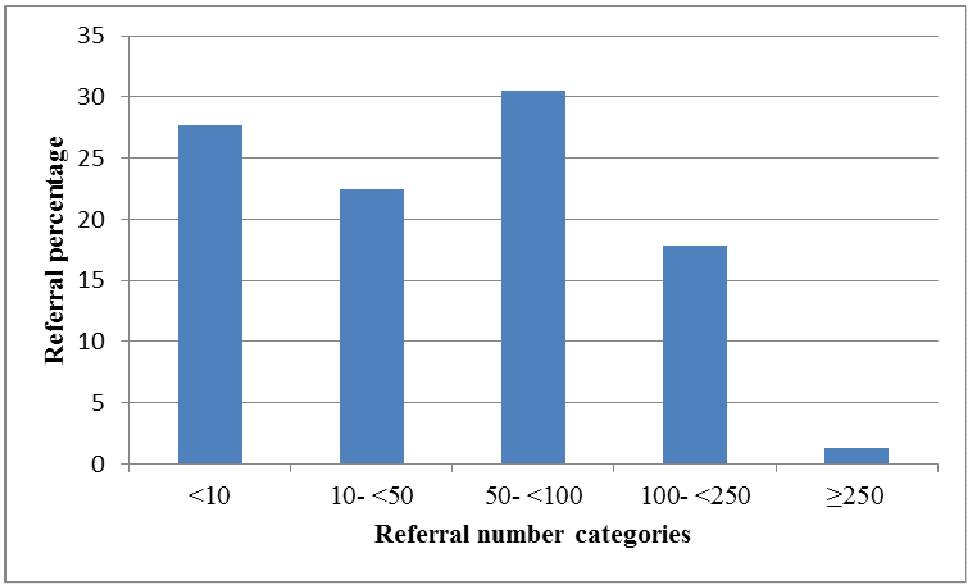

Figure 3-4 Number of referred patients to the GCWMS from 2008-2014 by GP practice code.

3.4.2 Referral and baseline characteristics

3.4.2.1 Referral

Of the 23,650 patients referred between 2008 and 2014 (**Table 3-2** shows baseline characteristics), the highest proportion of patients referred were aged between 40-59 years (47.8%). The majority of these referred patients were woman (71.1%), the mean age was 46.2 years and the men were older than women (mean ages 49.0 and 45.1 years, respectively). The majority of the patients were in the most deprived quintile of SIMD (47.4%) with only 9.8% in the least deprived quintile. The mean initial weight at referral was 111.2 kg, range 25-286 kg. BMI was also high; the mean BMI at referral was 40.6 kg/m^2, and the range 15.1-112.5 kg/m^2. Patients with a BMI lower than 30 kg/m^2 were then excluded due to invalid data. Most of the patients had a BMI between 35 and <50 kg/m^2 (76.4%). 18.4% and 13.4% of the patients had diabetes and hypertension, respectively.

	N=23,650		N=13,255 (56%)		N=7,329 (31%)		
Variables	**At referral**		**At assessment**		**At first visit**		**Ref/ 1visit**
Age	N	%	N	%	N	%	%
18-29	3,624	**15.3**	1,635	**12.3**	671	**9.2**	18.5
30–39	3,950	**16.7**	2,066	**15.6**	1,050	**14.3**	26.5
40–49	5,816	**24.6**	3,296	**24.9**	1,821	**24.8**	31.0
50–59	5,482	**23.2**	3,241	**24.5**	1,946	**26.6**	35.5
60–69	3,455	**14.6**	2,152	**16.2**	1,374	**18.7**	39.5
≥70	1,204	**5.1**	721	**5.4**	437	**6.0**	36.0
Missing	119	**0.5**	144	**1.1**	30	**0.4**	
Gender							
Male	6,778	**28.7**	3,693	**27.9**	1,979	**27.0**	29.0
Female	16,823	**71.1**	9,543	**72.0**	5,345	**72.9**	31.5
Missing	49	**0.2**	19	**0.1**	5	**0.1**	
SIMD							
Most deprived	11,206	**47.4**	5,738	**43.3**	2,966	**40.5**	26.5
2	4,427	**18.7**	2,480	**18.7**	1,410	**19.2**	32.0
3	3,101	**13.1**	1,884	**14.2**	1,099	**15.0**	35.5
4	2,456	**10.4**	1,497	**11.3**	891	**12.2**	36.0
Least deprived	2,321	**9.8**	1,495	**11.3**	924	**12.6**	40.0
Not known	139	**0.5**	161	**1.2**	39	**0.5**	
BMI							
30–34.9	3,393	**14.3**	1,464	**11.0**	840	**11.5**	24.5
35–39.9	8,934	**37.8**	4,620	**34.9**	2,346	**32.0**	26.0
40–49.9	9,124	**38.6**	5,576	**42.1**	3,197	**43.6**	35.0
≥50	2,032	**8.6**	1,501	**11.3**	946	**12.9**	46.5
Missing	167	**0.7**	94	**0.7**			
Weight kg							
<75	327	**1.4**	119	**0.9**	44	**0.6**	13.5
75–99	7,268	**30.7**	3,700	**27.9**	1,930	**26.3**	26.5
100–124	10,373	**43.9**	5,850	**44.1**	3,252	**44.4**	31.5
125–149	4,335	**18.3**	2,669	**20.1**	1,558	**21.3**	36.0
≥150	1,345	**5.7**	917	**6.9**	545	**7.4**	40.5
Missing	2	**0.0**					
Diabetes							
No	19,287	**81.6**	10,563	**79.7**	5,757	**78.6**	30.0
Yes	4,363	**18.4**	2,598	**19.6**	1,572	**21.4**	36.0
Missing			94	**0.7**			
Hypertension							
No	20,492	**86.6**	10,211	**77.0**	6,139	**83.8**	30.0
Yes	3,158	**13.4**	2,950	**22.3**	1,190	**16.2**	37.6
Missing			94	**0.7**			

Table 3-2 Characteristicsof patients at referral, assessment and at first visit.

3.4.2.2 Attendance

In total, 7,329 participants attended at least 2 sessions and their characteristics can be seen in **Table 3-2**. The average weight of those patients who attended at least one session was 115.2 kg (range 52.6 to 271.9 kg), (129.2 kg in men and 109.9 kg in women). The mean BMI in the first session of the lifestyle phase was 42.2 kg/m^2 (range 30.04 to 85 kg/m^2), (42.0 in men and 42.3 in women). The majority of the patients had a BMI between 35 and <50 kg/m^2 (75.6%), and nearly (70.7%) of patients weighed between 75 to 124 kg. 72.9% of the patients present at the first session were females, and in the most deprived quintile (40.5%) of the SIMD with only (12.6%) in the least deprived quintile. 21.4% and 16.2% of the patients at the first session respectively suffered from diabetes and hypertension.

3.4.2.3 Opt in rate

Table 3-2 shows just 31% of the total referred patients attended at least 2 sessions. There was a low opt in rate for young people compared with old people, as only 18.5% of the referred patients aged from 18-29 years attended ≥2 sessions, whereas 39.5% of referred patients aged (60-69 years) attended at least 2 sessions. In total, 31.5% and 29.0% of the referred females and males respectively attended the first session. There was a slightly higher opt in rate from referral to first session found for those from the highest quintile of SIMD versus the lowest (40.0% vs. 26.5%). Furthermore, the opt in rate was higher among heavier people than lighter ones; for example, 46.5% of the referred patients with a BMI ≥50kg/m^2 turned up compared to 24.5% of those with BMI =34.9 kg/m^2. Therefore,

more than 100 kg, or with a BMI of more than 40 kg/m^2, had a higher opt in rate. Just 36.0% and 30% of the referred patients with and without diabetes respectively attended the first session. Moreover, 37.6% of the referred patients with high blood pressure turned up; whereas, 30.0% of referred patients with normal blood pressure attended ≥2 sessions. Likewise, those with diabetes or hypertension had a higher opt-in rate than the patients without diabetes and those with normal blood pressure.

3.4.2.4 BMI classification for individuals attending at least one session

Nearly two thirds (56.2%) of the 8,173 GCWMS patients referred between 2008-2014 and who attended at least one session had a baseline BMI ≥40 kg/m^2; the distribution of BMI data is positively skewed **(Figure 3-5)**, and according to WHO groups (2014b), this percentage of patients are classified as class III obese **(Table 3-3)**.

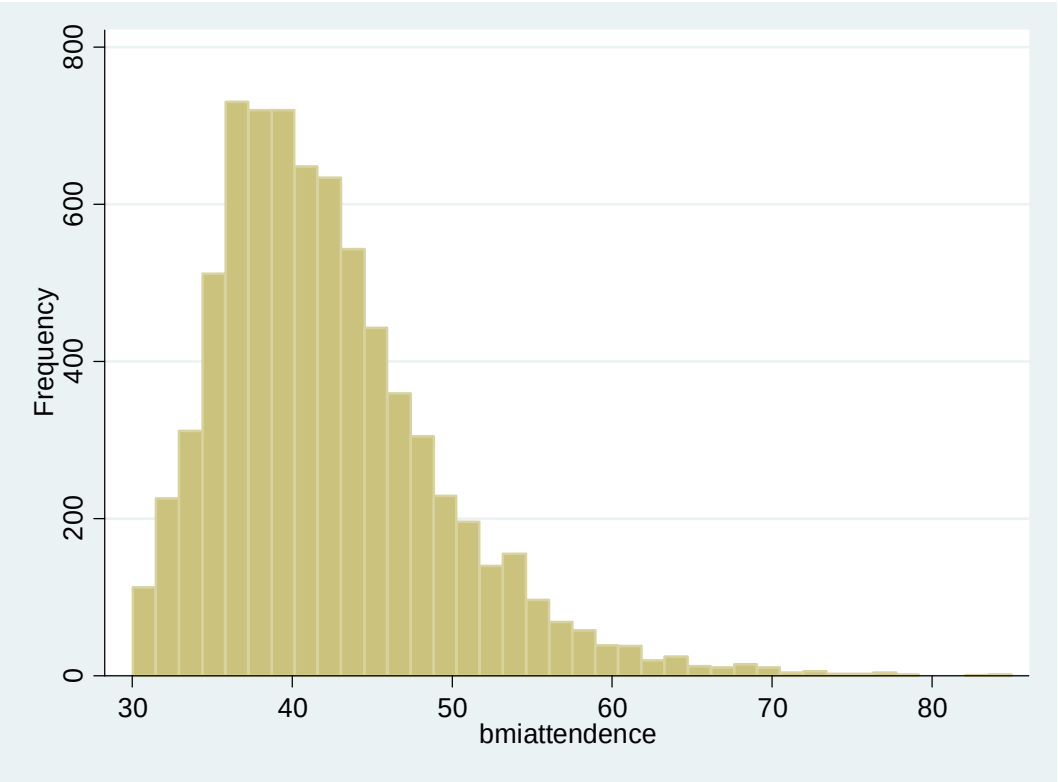

Figure 3-5 Histogram of baseline BMIs among 8,173 patients attending the GCWMS, 2008-2014.

Obesity classes	Frequency	Percentage
30-34 Class I	939	11.4
35-39 Class II	2,633	32.2
>=40 Class III	4,601	56.2
Total	8,173	100

Table 3-3 Baseline Body Mass Index of the 8,173 GCWMS patients, 2008-2014.

3.4.3 Weight loss outcomes

3.4.3.1 Completers and non-completers

In total, 4,042 patients (55.1%) completed the lifestyle programme, attending 80% of the total sessions. A higher proportion of men completed the lifestyle programme than women, almost 60% and 53% respectively. In addition, the proportion of patients from the most affluent areas was higher than from the most deprived areas in cases of programme completion (62% vs. 51.8%). Age ≥30 years, BMI ≥50 kg/m^2 and weight ≥150 kg were associated with a greater proportion of programme completion. In addition, a higher proportion of patients with diabetes and hypertension completed the programme (57.8% and 57.0%, respectively) compared to patients who are obese without diabetes or hypertension **(Table 3-4)**.

			Total (completers & non-completers) (attended at least 2 sessions)				Completers (subgroup of total) (attended at least 7 sessions)			
		N	**Mean weight change and 95% CI**	***P*-value**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**	**N (%) of total**	**Mean weight change and 95% CI**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**
All		**7,329**	-3.58 (-3.6 to -3.4)		2,232 (30.5%)	1,874 (25.5%)	**4042** (55.1)	-5.09 (-5.2 to -4.9)	1,854 (46%)	1,591 (39.5)
Gender	Male	1,979	-4.51 (-4.7 to -4.2)	0.001	762 (38.5)	575 (29)	1186 (59.9)	-6.14 (-6.4 to -5.8)	643 (54)	499 (42)
	Female	5,345	-3.23 (-3.3 to -3.1)		1468 (27.5)	1297 (24)	2853 (53.3)	-4.65 (-4.8 to -4.4)	1209 (42)	1090 (38)
	Missing	5					3			
SIMD	1 (most deprived)	2,966	-3.32 (-3.4 to -3.1)	0.001	847 (28.5)	703 (24)	1537 (51.8)	-4.91 (-5.1 to -4.6)	690 (45)	589 (38)
	2	1,410	-3.60 (-3.8 to -3.3)		448 (32)	381 (27)	786 (55.7)	-5.17 (-5.4 to -4.8)	379 (48)	324 (41)
	3	1,099	-3.67 (-3.9 to -3.4)		336 (30.5)	283 (26)	614 (55.8)	-5.06 (-5.4 to -4.6)	274 (44.5)	234 (38)
	4	891	-3.80 (-4.0 to -3.5)		279 (31)	235 (28.5)	513 (57.5)	-5.30 (-5.7 to -4.8)	235 (46)	204 (40)
	5 (least deprived)	924	-4.06 (-4.3 to -3.7)		312 (34)	262 (28.5)	573 (62)	-5.30 (-5.6 to -4.9)	268 (47)	232 (40.5)
	Missing	39					19			
Age	≤29	671	-2.27 (-2.6 to -1.9)	0.001	140 (21)	103 (15)	288 (42.9)	-3.84 (-4.4 to -3.2)	104 (36)	81 (28)
	30-39	1,050	-3.41 (-3.6 to -3.1)		309 (29.5)	240 (23)	536 (50.9)	-5.15 (-5.5 to -4.7)	254 (47)	201 (37.5)
	40-49	1,821	-3.62 (-3.8 to –3.4)		563 (31)	453 (25)	974 (53.1)	-5.47 (-5.7 to -5.1)	474 (48.5)	395 (40.5)
	50-59	1,946	-3.82 (-4.0 to -3.6)		627 (32)	523 (27)	1108 (56.9)	-5.22 (-5.5 to -4.9)	518 (47)	436 (39)
	60-69	1,374	-3.94 (-4.1 to -3.7)		458 (33)	418 (30.5)	849 (61.7)	-5.10 (-5.3 to -4.8)	390 (46)	361 (42.5)
	≥70	437	-3.59 (-4.0 to -3.1)		127 (29)	129 (29.5)	272 (62.2)	-4.50 (-4.9 to -4.1)	108 (40)	110 (40.5)
	Missing	30					15			
Male	≤29	109	-3.75 (-4.7 to -2.7)	0.56	39 (36)	23(21)	52 (47.7)	-5.70 (-7.3 to -4.0)	26 (50)	18 (34.5)
	30-39	211	-4.24 (-5.0 to -3.4)		78 (37)	49 (23)	113 (53.5)	-6.25 (-7.3 to -5.1)	65 (57.5)	41 (36)
	40-49	449	-4.64 (-5.1 to -4.1)		168 (37.5)	123 (27.5)	247 (55)	-6.88 (-7.6 to -6.1)	144 (58)	107 (43)
	50-59	599	-4.55 (-4.9 to -4.1)		232 (39)	178 (30)	358 (59.7)	-6.23 (-6.8 to -5.6)	192 (53.5)	150 (42)
	60-69	481	-4.69 (-5.1 to -4.2)		194 (40)	155 (32)	327 (67.9)	-5.79 (-6.3 to -5.2)	173 (53)	142 (43.5)
	≥70	117	-4.30 (-5.0 to -3.6)		46 (39)	43 (37)	81 (69.2)	-5.07 (-5.9 to -4.2)	39 (48)	37 (45.5)
	Missing	12					8			

			Total (completers & non-completers) (attended at least 2 sessions)				Completers (subgroup of total) (attended at least 7 sessions)			
		N	**Mean weight change and 95% CI**	***P*-value**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**	**N (%) of total**	**Mean weight change and 95% CI**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**
Female	≤29	562	-1.98 (-2.2 to -1.6)	0.001	101 (18)	80 (14)	236 (41.9)	-3.43 (-4.0 to -2.8)	78 (33)	63 (26.5)
	30-39	839	-3.22 (-3.5 to -2.9)		231 (27.5)	191 (23)	423 (50.4)	-4.85 (-5.3 to -4.4)	189 (44.5)	160 (38)
	40-49	1,372	-3.29 (-3.5 to -3.0)		394 (29)	329 (24)	725 (54.8)	-4.98 (-5.3 to -4.6)	329 (45.5)	287 (39.5)
	50-59	1,347	-3.48 (-3.6 to -3.2)		394 (29)	344 (25.5)	749 (55.6)	-4.72 (-5.0 to -4.4)	325 (43.5)	285 (38)
	60-69	893	-3.54 (-3.7 to -3.3)		264 (29.5)	263 (29.5)	522 (58.4)	-4.66 (-4.9 to -4.3)	217 (41.5)	219 (42)
	≥70	320	-3.33 (-3.7 to -2.9)		81 (25)	86 (27)	191 (59.6)	-4.26 (-4.6 to -3.8)	69 (36)	73 (38)
BMI	30–34.9	840	-2.93 (-3.2 to -2.6)	0.001	193 (23)	220 (26)	468 (55.7)	-4.09 (-4.4 to -3.7)	163 (35)	187 (40)
	35–39.9	2,346	-3.34 (-3.5 to -3.1)		668 (28.5)	643 (27.5)	1258 (53.6)	-4.86 (-5.0 to -4.6)	561 (44.5)	542 (43)
	40–49.9	3,197	-3.66 (-3.8 to -3.5)		994 (31)	775 (24)	1754 (54.8)	-5.17 (-5.3 to -4.9)	818 (46.5)	657 (37.5)
	≥50	946	-4.44 (-4.7 to -4.1)		377 (40)	236 (25)	562 (59.4)	-6.18 (-6.6 to -5.7)	312 (55.5)	205 (36.5)
Weight	<75	44	-2.19 (-3.4 to -0.8)	0.001	5 (11.5)	12 (27)	21 (47.7)	-3.27 (-4.0 to -2.5)	4 (19)	9 (43)
	75–99	1,930	-2.86 (-3.0 to -2.6)		440 (23)	503 (26)	1033 (53.5)	-4.08 (-4.3 to -3.8)	370 (36)	417 (40.5)
	100–124	3,252	-3.48 (-3.6 to -3.3)		969 (30)	831(25.5)	1765 (54.2)	-4.88 (-5.0 to -4.6)	791 (45)	697 (39.5)
	125–149	1,558	-4.12 (-4.3 to -3.9)		575 (37)	377 (24)	899 (57.7)	-5.88 (-6.2 to -5.5)	489 (54.5)	340 (38)
	≥150	545	-5.23 (-5.6 to -4.8)		243 (44.5)	151 (27.5)	324 (59.4)	-7.32 (-8.0 to -6.5)	200 (61.5)	128 (39.5)
Diabetes	No	5,757	-3.67 (-3.7 to -3.5)	0.001	1801 (31)	1496 (26)	3133 (54.4)	-5.26 (-5.4 to -5.0)	1487 (47.5)	1270 (40.5)
	Yes	1,572	-3.24 (-3.4 to -3.0)		431 (27.5)	378 (24)	909 (57.8)	-4.4 (-4.7 to -4.2)	367 (40.5)	321 (35.5)
Hypertension	No	6,139	-3.53 (-3.6 to -3.4)	0.03	1844 (30)	1560 (25.5)	3364 (55)	-5.01 (-5.2 to -4.9)	1547 (46)	1331 (39.5)
	Yes	1,190	-3.83 (-4.0 to -3.5)		388 (32.5)	314 (26.5)	678 (57)	-5.08 (-5.4 to -4.7)	307 (45)	260 (38.5)

Table 3-4 Subgroup analyses for the lifestyle phase of the GCWMS, using the LOCF method. First referrals from 2008 to 2014 inclusive (*n* =7,329). *P*-values were determined by using a t-test and ANOVA test (*p*-value <0.05 considered statistically significant) (CI: Confidence Interval; N: Number).

After completing the lifestyle intervention programme, the results showed completers (those attending at least 7 sessions) had greater weighted losses than non-completers (those attending fewer than 7 sessions). The mean weight change and 95% CI in completers and non-completers was -5.09 kg (95% CI: -5.2 to -4.9 kg) and -1.72 kg (95% CI: -1.8 to -1.6 kg), respectively. In addition, the mean weight change in completers and all patients (total) was -5.09 kg and -3.58 kg respectively. By the end of the lifestyle phase, almost 55% of patients who attended at least two sessions, also attended at least seven sessions; and of these 'completers', 46% lost 5 kg or more. 30.5% of all patients (7,329) lost at least 5 kg at the end of the lifestyle phase **(Table 3-5)**. Appendix 1 represents the mean weight change by the number of sessions attended, in order to establish whether a smaller number of sessions attended by the patients could lead to a clinically significant weight loss. Those who attended more sessions achieved a greater weight loss than the participants who attended fewer sessions.

	N	%	Mean weight change and 95% CI (kg)	Lost ≥5 kg	Lost ≥5%
Phase 1 (total)					
Completers (≥7 sessions)	4,042	55.1	-5.09 (-5.2 to -4.9)	1,854 (46%)	1,591 (39.5%)
Non-completers (<7 sessions)	3,287	44.8	-1.72 (-1.8 to -1.6)	378 (11.5%)	283 (8.5%)
Total (All) (≥2 sessions)	**7,329**		-3.58 (-3.6 to -3.4)	2,232 (30.5%)	1,874 (25.5%)
Overall % success	**23,650**	-	-	9.4%	8%

Table 3-5 Weight loss at the end of the lifestyle phase from the first session in the same phase and the overall % success for referred patients (CI: Confidence Interval).

3.4.3.2 Sex, age and SIMD

Generally, men were more successful at achieving the 5 kg target weight loss (mean losses in men and women were 4.51 and 3.23 kg, respectively). Patients in the least deprived quintile lost more weight in both groups (completers and others) than the patients in the most deprived quintile did; however, deprivation did not appear to affect the proportion losing their target weight. The success rates for weight loss for men in all age groups, ranging from 30 to 70 years, were around 40% (37 to 40%) compared to around 30% (27.5 to 29.5%) in women. Young men and young women had less success; 36% men vs. 18% of women aged under 30 years achieved 5 kg weight loss.

3.4.3.3 Initial BMI, diabetes and hypertension

Those patients who were heaviest (BMI ≥50 kg/m^2 and weight ≥150 kg) achieved the greatest proportion of individuals losing 5 kg or more (40% and 44.5%). Patients with diabetes were less likely to achieve the ≥5 kg target weight loss (27.5% for those with diabetes and 31% for those without); the total mean weight change, and 95% CI in people with diabetes and people without diabetes were -3.24 kg (95% CI: -3.4 to -3.0 kg) and -3.67 kg (95% CI: -3.7 to -3.5 kg) respectively. On the other hand, participants with hypertension were generally more successful at losing the 5 kg target weight than patients without hypertension (the mean weight change of 95% CI in patients with and without hypertension was -3.83 kg (95% CI: -4.0 to -3.5 kg) and -3.53 kg (95% CI: -3.6 to -3.4 kg), respectively.

3.4.3.4 Target weight loss (5 kg and 5%)

5 kg and 5% weight loss were looked at as these targets are mentioned in the guidelines (SIGN 115, 2010). Therefore, in terms of meeting the 5 kg and 5% weight loss target, male patients performed better than female patients with a 38.5% losing ≥5 kg and 29% ≥5% when compared to 27.5% losing ≥5 kg and 24% ≥5%. However, young men and young women (≤29 years) had the lowest proportion of individuals losing their target 5 kg or more. The heaviest participants (≥50 kg/m^2) comprised the greatest proportion (40%) of individuals losing 5 kg or more, compared with the lighter individuals (≤35 kg/m^2). Individuals without diabetes and those with hypertension were more successful at losing ≥5%. In total, 55.1% of those participants who started GCWMS completed the lifestyle phase programme, and of those, 39.5% had lost 5% or more of their initial weight. Overall,

among all the patients who attended at least 2 sessions, 25.5% lost ≥5% of their initial body weight **(Table 3-5)**.

3.4.3.5 Overall percentage success

Of the 23,650 participants who were referred to the GCWMS between 2008-2014, 9.4% of patients lost at least 5 kg and 8% lost ≥5% of their starting weight (Table 3-5).

3.5 Summary of the main findings

- There was a low number of referrals from each health practice across the six-year duration studied; 27.7% of the total GPs had <10 referrals.
- Many people referred to the GCWMS never attended, with only 31% of referred patients attending their first session.
- The majority of those referred were women, from the most deprived areas, with BMIs between 35 and 50 kg/m^2, did not have diabetes and had blood pressure within the normal range.
- Half of the patients attending at least one session were classified as class III obese.
- A higher proportion of men, those from the least deprived areas, those who were older and those with a higher initial body weight completed the lifestyle programme.
- Patients aged 60-69 years, men, those from the least deprived areas, those with higher BMIs, those with high blood pressure, and individuals without diabetes were more likely to lose 5 kg.
- This lifestyle (phase 1) programme was effective at achieving 5 kg weight loss, but only for fewer than 50% of the patients who completed the lifestyle phase. A greater proportion of those completing the programme (attended ≥7 sessions) lost their target (≥5 kg) compared with non-completers.
- In terms of the % success for all patients referred to GCWMS, 9.4% and 8% lost 5 kg and 5%, respectively.

3.6 Discussion

This research evaluated the first phase (lifestyle) of GCWMS (*n* =7,329). The service's established goal is for attendees to achieve at least a 5 kg weight loss, because there is evidence that moderate weight loss of 5–10 kg is associated with significant clinical benefits in individuals with obesity (Avenell *et al*., 2004). This research evaluated the effectiveness of the lifestyle phase of this large weight management programme by reporting the proportion of patients who lost at least 5 kg of weight during the lifestyle phase. Overall, the study found that 9.4% of all the patients referred lost at least 5 kg and 30.5% of the participants who attended at least 2 sessions lost ≥5 kg. Among those patients who completed the lifestyle phase, over 46% achieved their target weight loss.

3.6.1 GP practice referral

There was a variation between the numbers of referrals from each GP practice. Low referral rates from the majority of GPs practices will not have occurred due to a lack of with obesity needing a weight management programme. The Scottish Health Survey (2011) reported that 24% of adults in Glasgow are obese; therefore, the possible reasons might have been patients preferring not to enrol in a weight management programme, or GPs' lack of concern or interest in the programme. In addition, GPs might have preferred to avoid disputes with patients because of the unsuccessful overall percentage weight loss among referred patients, as fewer than 10% lost ≥5% of their initial weight. It is important to consider that the practice size and location may influence the number of referrals.

A previous qualitative study explored GPs' views about managing patients with obesity (21 GPs from 15 different practices in London); it concluded that GPs believe obesity management to be the patient's responsibility, and so are unwilling to offer medical solutions (Epstein and Ogden, 2005). A further qualitative study (conducted in Portugal and interviewed 16 GPs) reported that GPs are frequently negative when discussing their role in treating patients with obesity (Teixeira *et al*., 2015). The majority of GPs believe that they will struggle to make any improvements simply by advising their patients to adopt long term lifestyle changes. GPs also commented on some barriers, such as lack of patient motivation, insufficient time allocated to counselling, lack of training, and communication problems with patients when talking about their weight. Additional previous studies have reported that 83% of GPs would raise weight as a problem with patients who are obese, but only 15% discussed weight management with them (Laws,

2004). Overall, the existing research found that GPs think the main cause of obesity is eating too much, an issue that is within patients' control. The recommendations about what could be done to help motivate GPs' and other primary care staff on this issue are discussed in Chapter 7.

3.6.2 Referred patients' characteristics

In order to examine how representative the referred population to those who were eligible in NHS Greater Glasgow and Clyde, data from the Scottish Health Survey (2008-2011) were examined by another researcher (Daniel Slack, abstract in UKCO, 2015). A total of 40% of the eligible population were men, of whom only 28.6% were referred to the GCWMS; and there was an over-representation of younger adults (aged 18-29) and those with a higher BMI. A total of 15.3% of the referred participants were aged 18-29 compared with 5.9% of the eligible population; 8.6% of those with a BMI >50 kg/m^2 were referred, compared to 0.7% of the eligible population. However, it was found that the spread of deprivation was similar in both the eligible population and the participants referred to the GCWMS, which might indicate that they have greater need and fewer resources.

Despite prevalence of obesity in both sexes being similar, just 28.7% (*n* =6,778) of all patients (*n* =23,650) referred to the GCWMS from 2008 to 2014 were men. Similarly, only 18.5% of the referrals to a North Somerset scheme, 10.5% to Weight Watchers and 10.7% to Slimming World audits were for men (Dixon *et al*., 2012); leading to the conclusion that fewer men are referred to UK weight management centres. This research shows that the majority of the referred individuals were women (71.1%), indicating a reluctance among men to enrol in a lifestyle programme, or a reluctance among clinicians to refer men; this is consistent with the previous research (89.3% of the referred patients were women in Stubbs *et al*., 2011 and 81.5% in Dixon *et al*., 2012). Additionally, this finding concurs with another study that reported 73.7% of participants referred to Special Lifestyle Management (SLiM) were women.

A previous study evaluated the rate of weight loss for 34,271 participants referred for a 12-week course of Slimming World sessions (Stubbs *et al*., 2011). Of the referred patients, 89% were women, and it has been suggested this might be because this programme failed to recognise gender concerns.

Other suggested reasons might be the fact that more men are in full-time employment (38%) compared with female (25%) (The Scottish Government, 2012) and therefore cannot commit to attending regular daytime appointments, or because the associations for men with increasing body size differ from those for women (i.e. men who are overweight and obese are generally less interested in their weight than their female counterparts (Gray *et al*., 2009; Stibb, 2004). Moreover, in case of illness, men are less likely to consult a physician and also generally less likely to participate in health services offered (Mansfield *et al*., 2003). A previous systematic review of the evidences for the management of obesity in men was funded by the Health Technology Assessment programme in the UK, and recommended providing a weight management programme in social places, such as workplaces and sports clubs, to attract men to enrol in weight management programmes (Robertson *et al*., 2014). In addition, according to the predictions of the Foresight report more men than women are overweight or obese; thus, further alterations to practices are needed to increase referral rates for men and to establish why men do not engage with weight management programmes (Government Office for Science, 2007).

This research and previous findings in the two studies that evaluated the GCWMS show that most of the referred individuals were from the most deprived areas (47.4%), compared to those from the most affluent areas; (62% in Morrison *et al*. and 43.3% in Logue *et al.* studies). The reason might be because of the difficulties overcoming long term unhealthy food habits (Turrell *et al*., 2002) and their lower level of education (Drewnowski and Specter, 2004).

3.6.3 Opt-in and dropout rate

GCWMS offers longer term support, of up to two years, to individuals who choose to continue losing weight. However, some patients choose to leave the programme after the first or second month, possibly due to factors such as weight regain, failure to lose weight, or confidence brought about by their weight loss success, as they believe they can follow the same treatment plan at home independently without the assistance of the service. This explains the reasons for the missing data and using the LOCF method. A previous study (*n* =124), which recruited patients with BMI >30 kg/m^2 from outpatients' clinic in Croatia or via GP referral to a weight management study for 12 months, was performed to identify factors that predict dropout rates. This study found the overall drop rate was 32.3% and resulted from reasons ranging from lack of motivation (15.3%), to psychological problems or health-related issues (8.0%). Moreover, it was not possible to contact the patients (6.4%)

due to unhappiness with the programme (2.4%); in addition to their lower education level (Hadziabdic *et al*., 2015).

Young patients dropped out of the programme at a higher rate than older people (81.5% of young patients aged 18-29 years dropped out) and this result is consistent with previous findings of the multidisciplinary tier 3 of the Fakenham weight management service (FWMS) (Jennings *et al*., 2014). It was found that the mean age of participants who were assessed but not recruited was lower than those who attended (45.2 vs. 52.7 years, p =0.001). A possible explanation of this might be the priority given to family members and children or work commitments. Another possible explanation is insufficient weight loss reducing their motivation to attend sessions.

Moreover, patients from the most deprived areas were more likely to drop out, as only 26.5% of the total number of patients referred turned up. This could be due to a lack of transportation or the need to prioritise work. A higher proportion of patients with BMI ≥50 kg/m^2 had turned up, possibly due to their concern that their body weight was damaging their overall health. In contrast, a RCT (2 year's duration in the US) compared weight loss achieved through self-help weight loss and with a designed commercial programme (12 weeks), and suggested that most of the patients who dropped out had higher starting BMIs (Heshka *et al*., 2003). This discrepancy could be due to the difference in the BMI at baseline between the two studies for recruited patients; individuals with BMI ≥30 kg/m^2 were included in this research, whereas, Heshka *et al*.'s study included patients with BMI 27-40 kg/m^2. The RCT thus stopped at BMI =40 kg/m^2, while the current study includes patients with much higher BMIs, some with BMI of >50 kg/m^2.

A further interesting finding was that referred patients with hypertension and diabetes had a higher likelihood of turning up (37.6% and 36% respectively), compared with people without hypertension and without diabetes (30% and 30% respectively). It seems possible that this result is due to high blood pressure being an age-related problem and therefore as more older individuals turned up than younger ones; this creates the illusion of a highly significant effect. Another possible explanation, however, might be that a diagnosis of hypertension and diabetes heightened patients' anxieties regarding their general health.

3.6.4 Completion rate

Some studies have used the higher threshold of 80% to define programme completion; this was consistent with the current research (Stubbs *et al*., 2011; Dixon *et al*., 2012). Elsewhere, previous studies have applied a lower threshold and defined completed cases as participants who attended four or more appointments in 3 months, five or more sessions in 6 months, or six or more sessions in 12 months (McCombie *et al*., 2012); defining completers as those who attended at least half the sessions (Morrison *et al*., 2011; Logue *et al*., 2014). Studies using the current threshold for completion (80%) may lead to a more accurate reflection of the true effectiveness of weight management programmes when compared with studies that define completion as attendance of 50% of the sessions. However, lower thresholds (around the 50% attendance rate) are a more realistic reflection of the median number of sessions attended by patients and therefore these studies using these lower thresholds include more patients when compared to studies using higher thresholds (80%) that then tend to focus on individuals that achieve higher weight losses. 80% is equivalent to the threshold of drug adherence used in the majority of medication trials as they wish to measure the effect of exposure to the full course of treatment; by using 80% attendance then it is ensuring exposure to the full course of behavioural treatment. The research results show a significant difference in completion rates between the sexes; men who completed the programme achieved their target weight loss. Stubbs *et al*. (2011) and Brown *et al.* (2015) reported completion rates of 57.4% in Slimming World and 55.2% in SLiM respectively among women (compared with 53.3% in the current research).

55.1% of the participants who attended at least 2 sessions completed the treatment programme. This research shows a low completion rate in younger participants and those in the most deprived quintile, which is consistent with the finding of a previous randomised trial (Heshka *et al*., 2003). In terms of comparing completion rate with other services, 56% of SLiM patients completed a 6 month course of treatment (Brown *et al*., 2015); and from the Lighten Up RCT at 3 months duration, 66%, 63% and 64% of participants completed the Weight Watchers, Sliming World or Rosemary Conley programmes (Jolly *et al*., 2011). Another study reported that out of 34,271 participants referred to Sliming World between 2004 and 2009, those who attended 12 sessions over a three-month period; totalled 58.1%, where programme completion was measured by attendance at minimum of 10 sessions out of 12 (Stubbs *et al*., 2011). In conclusion, the

completion rate at GCWMS was low but consistent with other services; hence, this is a problem of all services and an area that needs further improvement.

3.6.5 Weight loss outcomes and comparison with other weight management programmes

To the best of our knowledge, this research is one of very few examples of an evaluation of the effectiveness of a lifestyle intervention made by a specialist weight management programme targeting subjects who are obese with BMI ≥30 kg/m^2. The research findings show that the NHS GCWMS achieved a 5 kg weight loss in 30.5% of participants following the lifestyle intervention. This equates with 25.5% of participants losing 5% of their initial body weight when a LOCF analysis is used, as the mean weight was greater than 100 kg at baseline. In total, 46% of participants who completed the programme achieved at least 5 kg weight loss and 39.5% of the individuals lost 5% of their weight.

In comparison with an earlier study by Morrison *et al.* (2011), which evaluated the lifestyle phase of all patients referred to the GCWMS between 2004 and 2006, 13.6% of patients who opted into the programme lost at least 5 kg compared with 30.5% in the current research. 35.5% of the patients completing the programme lost at least 5 kg, compared with 46% in this study. Additionally, a previous BMJ paper by Logue *et al*. (2014), which evaluated the GCWMS (2008-2009) over 12 months, reported that 26% of patients who opted in and 36% of those completing the programme had lost ≥5 kg at the end of the lifestyle phase. These results are better than the results obtained in the earlier two studies; this might be attributable to the fact that as the patient figures spanned 6 years (2008-2014) the service may have improved over time. Another reason why the results are better might be that a higher threshold for completion than that used in previous studies was used in this study. As attendance is linked with successful weight loss, higher thresholds will selectively detect participants with higher weight losses. This will not affect all the patients included in the study; however, this research included participants who attended at least 2 sessions, whereas the other two papers included all the patients who attended ≥1 session.

In comparing the current results of the GCWMS with the other tier 3 weight management programme, the following table summarises the results of the three different weight management services (GCWMS, FWMS, and SLiM):

Results	GCWMS	FWMS	SLiM
Mean age (years)	46.2	52.7	48.2
Sex (% of females)	71.1	70	73.7
Initial weight (kg)	115.2	124.4	135
Initial BM (kg/m^2)	42.2	44.1	49.1
Mean weight change (kg)	-3.58 after 4 months	-3.6 after 3 months	-4.1 after 6 months
≥5% weight loss (%)	25.5 after 4 months 39.5 (completers)	25.2 after 3 months 34.2 (completers)	24.9 after 6 months 32.3 (completers)
Dropout rate (%)	44.8 after 3 months	14.3 after 6 months	44 after 6 months
Completion definitions	Attended ≥7 sessions over 4 months	Attended all the sessions (10-15 sessions) over 1 year	Attended all sessions (6 sessions) over 6 months

Table 3-6 Summary of the results from three different weight management programmes (tier 3).

In comparison with the SLiM programme in Birmingham, a total of 828 participants with BMI ≥35 kg/m^2 with comorbidity or ≥40 kg/m^2 without comorbidity were enrolled between 2009 and 2013, within SLiM over 48 months duration (Brown *et al*., 2015). SLiM included monthly sessions over 6 months of lifestyle interventions and behavioural modification; and those who attended all 6 sessions were defined as completers. The mean weight change in the current study for all the participants (LOCF) was -3.58 kg (95% CI: -3.6 to -3.4 kg) over 4 months duration, compared with -4.1 kg (95% CI: -3.6 to -4.6 kg) for all the SLiM participants at 6 months duration. 25.5% by the end of the lifestyle phase of the current study, and 24.9% at the end of SLiM, achieved at least 5% weight loss, and this might be due to the higher mean weight (135 kg) and BMI (49.1 kg/m^2) at baseline for the SLiM patients. In cases of completion, the mean weight change was -3.7 and -5.5 kg (95% CI: -4.9 to -6.2 kg) at 3 and 6 months duration on the SLiM programme, compared to -5.09 kg (95% CI: -5.2 to -4.9 kg) for the GCWMS patients. Moreover, 44.4% and 32.3% of SLiM patients lost ≥5 kg and ≥5% of initial weight respectively, compared with 46% and 39.5% of GCWMS participants completing the programme. The completion rate for SLiM (56%) was very similar to that for the GCWMS; patients had a higher BMI at baseline

(49.1 kg/m^2), and hence a lower percentage weight loss. In conclusion, SLiM achieved a lesser result than the GCWMS; this might be due to the fact that SLiM comprises a lower intensity lifestyle treatment and patients with a higher BMI than GCWMS.

Additionally, in comparison with other multidisciplinary FWMS in primary care (more details about the service are given in Chapter 1, page 70), the mean weight change at 3 months duration for 218 participants was -3.6 kg and 25.2% of the participants lost at least 5% of initial weight. There are some similarities in the outcomes between this programme and the results of the current research; in addition, the patients had almost the same characteristics as the GCWMS participants. The FWMS included participants with BMI ≥30 kg/m^2 with co-morbidity or ≥40 kg/m^2; however, it provided monthly sessions and one-year outcomes were reported. Those included in the FWMS were heavier than the participants in the GCWMS (the mean weight at baseline was 124.4 kg vs. 115.2 kg). Some limitations can be noticed as the percentage of 5 kg weight loss was not reported, in addition, the FWMS was evaluated from the initial set up in August 2011 to August 2012, and this relatively shorter period may not reflect its ultimate effectiveness (Jennings *et al*., 2014).

Comparisons with other weight management service (tier 2 services) outcomes are reasonable, with caution, as tier 2 is also a lifestyle weight management programme. However, there were differences between the methods used and the duration of the studies, in addition to the higher BMIs of the GCWMS participants. The GCWMS participants had a mean BMI of 42.2 kg/m^2, which is higher than the Counterweight programme (BMI 37.1 kg/m^2) or the Lighten Up trials (33.9 kg/m^2 in Weight Watchers, 33.8 kg/m^2 in Slimming World, 33.4 kg/m^2 in Rosemary Conley and 33.1 kg/m^2 in GP subgroup). For instance, the Lighten Up RCT reported that the proportions of patients achieving 5% loss in body weight at one year follow-up in Weight Watchers, Slimming World, and Rosemary Conley were 31%, 21% and 26%, respectively (Jolly *et al*., 2011). Additionally, there were differences in the data collection procedures between the current research and the Lighten Up study, as they used patient self-reporting for final weight; and the data were from RCTs where the mean BMIs were below 38 kg/m^2.

A previous study that evaluated a multicomponent lifestyle modification of the Live Life Better Service in the UK, from the period April 2010 to 30 April 2013, reported that 26% of 242 participants had lost at least 5% of their initial weight after 12 weeks duration

(mean weight change was -4.9 kg). However, it recruited participants with BMI ≥35 kg/m^2 with a comorbidity or BMI >40 kg/m^2, which differ from the inclusion criteria for the current research. Unfortunately, this study did not report the proportion of patients who lost 5 kg and the outcomes for the completers to allow a comparison with the current data (Wallace *et al*., 2016).

Another recent study evaluated a tier 2 multi-component weight management programme on referral (WMOR) that was offered through NHS South Gloucestershire in the UK from October 2008 to November 2010 (Birnie *et al*., 2016). This programme included a 12 week course of sessions consisting of dietary advice, physical activity, and information on behavioural change. Participants were able to access group meetings of Weight Watchers as well as receiving vouchers for a 12 week course of supervised group sessions. The mean weight change for all participants (*n* =559) in the study was -3.7 kg (95% CI: -3.4 to 4.1 kg). This figure is higher than the current result, as 32% of all participants and 58% of patients who completed the WMOR programme lost ≥5% of their initial weight. The participants in the WMOR programme were lighter (BMI ≥28 kg/m^2 and co-morbidities) than the GCWMS participants, and the definition of course completion was higher than in the current research, which may explain the difference in the percentage weight loss.

Another study (*n* =29,326 from 2007 to 2009) evaluated the weight change among participants referred to Weight Watchers by the NHS in the UK. 33% of all patients, and 54% of those completed the programme and attended 12 sessions at Weight Watchers over 3 months lost ≥5% initial weight (Ahern *et al*., 2011). This might be due to the lower average BMI of the Weight Watchers' patients at baseline, as the average BMI in the study was 35.1 kg/m^2 and 42.2 kg/m^2 in GCWMS. Therefore, the most successful programme is Weight Watchers, possibly a result of the higher attendance levels it commands (Dixon *et al*., 2012). Only 36% of participants attended Slimming World completed the programme of treatment compared with 44.8% for Rosemary Conley and 56% for Weight Watchers. In contrast with GCWMS, the Weight Watchers programme not only provides group support and dietary counselling, but also offers a variety of food products that can be purchased from supermarkets. Additionally, it provides support through technological media such as smart phones and computers.

Compared with the initial experience of the application of a Counterweight programme (1,256 participants) (more information about the programme is provided in Chapter 1, page

68), the current research shows the mean weight loss after 16 weeks' duration was -3.58 kg; the mean weight change in the Counterweight programmes for patients at three months (*n* =599) was -3.4 kg (Laws, 2004). This equates to 25.5% and 25.3% of patients losing ≥5% of their initial weight in the GCWMS and Counterweight programmes respectively. Of the 47.6% of those completing the Counterweight programme by attending 4 out of 6 sessions, 28% had lost ≥5% of weight. However, 55.1% completed the lifestyle programme in GCWMS, and of these, 39.5% lost 5% or more of their initial weight. Therefore, when complete cases are considered, GCWMS is more successful than Counterweight programme in achieving 5% weight loss. The possible reasons may be due to the differences in completion rate, programme and methodological approach, and may be because the GCWMS patients were more motivated than Counterweight programme patients. It is relatively easy for Counterweight patients to attend appointments in a practice provided by practice nurses, whereas the GCWMS patients generally had to travel further to attend sessions, perhaps indicating higher motivation.

3.6.6 Weight loss outcomes for subgroups

3.6.6.1 Men and women

This research shows men lost more weight than women in terms of both absolute kg and 5% of body weight at baseline, which is consistent with others findings (Dixon *et al*., 2012; Morrison *et al*., 2011). A previous study (*n* =34,271) audited the rate and extent of weight loss for participants referred to the Sliming World in the UK between 2004 and 2009 for 12 weekly sessions. It found that the average weight change and percentage weight change for men and women were -5.8 kg (-4.9%) and -3.8 kg (-3.9%), respectively (Stubbs *et al*., 2011). This potentially may be related to men having on average a higher weight at baseline. In the HTA report, a previous systematic review of RCTs assessing UK interventions, examined the management of obesity in men only, or men and women in the same trial. It suggested that whilst it is apparently more difficult for men to join a weight loss programme in the first place, when they do opt in and embark on one, they are more conscientious in their approach (Robertson *et al*., 2014). Further work is needed to ensure the programme is more successful in women to improve overall retention.

3.6.6.2 BMI

A previous study (evaluating the lifestyle phase of GCWMS between 2004 and 2006) showed that individuals with BMI ≥50 kg/m^2 were more likely to complete a programme than those with BMIs between 35 and 39 kg/m^2, although they were no more likely to lose weight when they did (Morrison *et al*., 2011). While, the current research found the same results concerning completion status, it also revealed that those with BMI ≥50 kg/m^2 were more likely to lose 5 kg or more. In total, 23% of patients with a BMI=30-34.9 kg/m^2 and 40% of those with BMI ≥50 kg/m^2 lost at least 5 kg. It is likely the greater success among patients with higher BMIs was at least partially because nearly 60% completed ≥80% sessions.

The Counterweight Project Team (2008) evaluated the counterweight programme of 1,906 patients with BMIs ≥30 kg/m^2, or ≥28 kg/m^2, and with obesity-related comorbidities, from 65 UK general practices. They found that after 12 months duration of lifestyle change, the mean weight changes for participants with BMI <30 kg/m^2 and BMI >40 kg/m^2 were -1.87 kg (95% CI: -3.8 to -0.05 kg) and -4.6 kg (95% CI: -5.9 to -3.2 kg), respectively. This is in agreement with the current findings that show participants with a higher BMI lost more weight than those with a lower BMI. Moreover, the current result is consistent with a recent study reporting the weight outcomes in 1.3 million adults over 3 months attending the Slimming World programme in the UK (Stubbs *et al*., 2015). It was suggested that the absolute weight loss improved when increasing the BMI category (p <0.001), as the mean weight change was -3.1 kg, -3.9 kg, -4.5 kg and -5.4 kg for those with BMIs <30 kg/m^2, 30-34.9 kg/m^2, 35-39.9 kg/m^2 and ≥40 kg/m^2, respectively. This might be due to greater health concerns, and making radical changes to obvious bad eating habits.

3.6.6.3 Age

Young individuals (≤29 years) were less likely to complete the programme and lose weight than older participants. In total, 42.9% of those aged ≤29 years completed the programme and their mean weight change was -3.84 kg (95% CI: -4.4 to -3.2 kg), compared with 62.2% of those aged ≥70 years. Generally, participants aged ≥30 year from both sexes lost more weight than the group aged ≤29 years. This is broadly consistent with the results of the Counterweight programme study, which evaluated 642 participants attending the programme for 12 months (Counterweight Project Team, 2008). The mean weight change for those aged <25 year was -1.69 kg (95% CI: -4.8 to -1.4 kg), and -2.71 kg (95% CI: -3.5

to -1.9 kg) for those aged ≥65 years. In addition, an earlier evaluation paper published in the BMJ Open, which reported the outcomes over a 12 month period and evaluated the GCWMS phases, suggested that young men had the greatest success and young women the least success (Logue *et al*., 2014).

However, this research found that both young men and young women had the lowest levels of success in losing weight, although the difference was not statistically significant for the male group. The differences might be a result of the different types of intervention offered for the patients in phase 2 (FWL, pharmacotherapy or LCD), as the BMJ paper evaluated the three phases. In contrast, this research evaluated phase 1, and patients were only offered a lifestyle intervention. Moreover, this result concurs with an earlier study evaluating the lifestyle phase of the GCWMS over 2 years; this found 679 participants aged <40 years (31.1%) completed the treatment programme, compared with 42.9% in the age bracket ≥60 years. Respectively, 33.1% and 35.3% of patients aged <40 years and ≥60 years lost at least 5 kg in weight (Morrison *et al.*, 2011). As stated earlier, the possible reasons for this might be patients' reduced enthusiasm because they are not yet suffering from any health issues, and the greater priority given to family or work commitments.

3.6.6.4 SIMD

As stated above, the majority of patients referred were in the most deprived quintile. However, they were less likely to turn up, with only 26.5% doing so compared with 40% from the least deprived quintile. In addition, those in the least deprived quintile lost more weight than those in the most deprived quintile (-4.06 kg (95% CI: 4.3 to -3.7 kg) and -3.32 kg (95% CI: -3.4 to -3.1 kg)), respectively. In terms of programme completion, a higher proportion of patients from the least deprived quintile completed the programme, but there was no significant difference in weight loss in relation to socio-economic status. A total of 62% of patients in the least deprived quintile and 51.8% in the most deprived quintile completed the programme, and the mean weight change was -5.30 kg (95% CI: -5.6 to -4.9 kg) and -4.91 kg (95% CI: -5.1 to -4.6 kg). An evaluation of GCWMS by Morrison *et al*. (2011) that covered the years 2004 to 2006 found that 49.3% and 34.4% of the people in the least deprived quintile and the most deprived quintile completed the programme. Unfortunately, there were no data from other weight management programmes to compare the effect of SIMD with current results. A possible reason for the poor attendance and completion of the programme could, as stated earlier, be due to a lack of transportation or the need to prioritise work. The recommendation highlights approaches

to improve retention within the service for patients opted in from more deprived areas, such as providing education in the area itself, and providing transportation for individuals to attend appointments.

3.6.6.5 Diabetes

The current research shows the absence of diabetes was associated with increased mean weight loss; the mean weight change was -3.24 kg (95% CI: -3.4 to -3.0 kg) and -3.67 kg (95% CI: -3.7 to -3.5 kg) in patients with and without diabetes, respectively. This difference was statistically significant, *p*-value =0.001. This finding concurs with another study that evaluated the Counterweight programme over 65 GP practices delivering interventions to 1906 participants with a BMI ≥30 kg/m^2. It shows that the mean weight change in patients with 12 monthly data in a Counterweight programme was -3.30 kg (95% CI: -3.9 to -2.7 kg) in patients without diabetes and -1.63 kg (95% CI: -2.4 to -0.7 kg) in patients with diabetes (Counterweight Project Team, 2008). This may be due to the differences in dietary adherence or because some anti-diabetic drugs may cause weight gain. This is based on a good range of evidence showing that some anti-diabetic drugs, such as metformin, GLP-1 and SGLT2, might cause weight loss or no change in weight, whilst others, such as SUs and TZDs, may cause weight gain (Bonora, 2007; Krentz, 2008; Solini, 2015). Additionally, Wing *et al*. (1987) found that people who were overweight and suffered from type 2 diabetes (12 subjects: 6 men and 6 women) lost less weight than their spouse without type 2 diabetes. After a behavioural 20-weeks weight-control programme, the weight change in participants with and without type 2 diabetes was -7.5 kg and -13.4 kg, p <0.01, respectively.

In comparison with the SLiM programme**,** the mean weight change for patients with diabetes who completed the lifestyle intervention at GCWMS (*n* =909) was -4.4 kg (95% CI: -4.7 to -4.2 kg), compared with -5.7 kg for the SLiM patients with diabetes after six months (*n* =142). In addition, a recent pilot study (*n* =34) evaluated the clinical outcomes of a 12 week lifestyle intervention programme that was delivered in a primary care setting in the UK and recruited participants with type 2 diabetes or pre-diabetes. It was found that the mean weight change was -3.1 kg (±2.3) after three months (Huntriss & White, 2016).

The Via Christi Weight Management programme (VCWM) is another weight loss programme, established in 1994 in the US as a partner of the Health Management Resources (HMR) that offers medically supervised weight loss. The programme comprises

two phases: phase 1 (LCD with behavioural modification) and phase 2 (maintenance). In comparison with the VCWM, a previous study sought to determine the effect of a LCD and behavioural change programme (12 weeks) in weight change for patients who are obese (BMI $\geq$30 kg/m^2) with and without diabetes. From 2009 to 2010, 310 charts were reviewed for patients with and without diabetes enrolled in the VCWM in the US. Data were collected before and after participants underwent a programme of meal replacement and weekly physical activity over a 12 week period; the mean ages for patients with and without diabetes were 54 and 50 years respectively. It found that patients with diabetes lost an average of 11.7% of their initial body weight, compared with 12.5% in those without diabetes (Stanford *et al*., 2012). It could therefore be concluded from the above studies that people with diabetes were less successful at losing weight, possibly because of their use of anti-diabetic drugs, which is explored further in Chapter 6.

3.6.6.6 Hypertension

In this research, participants with hypertension were more successful at losing the 5 kg target weight, and the reason for this was not clear, as some anti-hypertensive medications can cause weight gain, such as beta-blockers and some may cause weight loss, such as the diuretic group. The current results show that patients with hypertension lost a greater weight than those without hypertension. This result appears to be consistent with another study that aimed to evaluate rates and predictors of weight loss among 2,906 participants with obesity in the US who received regular primary care from 2008 to 2011, and who achieved hypertension control over a year. It found that participants who were prescribed antihypertensive medication (OR: 1.37, 95% CI: 1.07 to 1.76) were more likely to achieve clinically significant weight loss, compared with participants without antihypertensive drugs (Ho *et al*., 2016). This might be a result of the increased concern of participants with hypertension about their health, leading to improved dietary adherence. In addition, as this study shows, older people were more likely to lose their target weight, in which case the results might be attributable to age interaction, as the mean age for patients with and without hypertension was 55.2 years and 43.8 years respectively. However, to date few studies have conducted detailed investigation into weight loss comparisons between patients with and without hypertension.

3.7 Target weight loss and clinical benefits

Currently, the GCWM target is to achieve a 5 kg weight loss. However, given the higher BMI of individuals in this specialist weight management service, 5 kg is equal to 4.2% of mean body weight (mean initial weight was 115.2 kg). Based on the SIGN guidelines, "weight loss targets should be based on the participants' comorbidities and risks, rather than their weight alone. As those with BMI 25-35 kg/m^2 are less likely to have obesity-related comorbidities, a 5-10% (5-10 kg) weight loss is needed to reduce the risk of metabolic disorders and cardiovascular disease. As obesity-related comorbidities are more likely to be present in patients with BMI >35 kg/m^2, a weight loss in excess of 15-20% will be required for comorbidity improvement" (SIGN 115, 2010).

A previous RCT that included subjects with BMI ≥27 kg/m^2 and aged 60 years or older, reported that a 5% weight loss was associated with reduced knee pain and improved physical function in patients with obesity and knee osteoarthritis (Bales and Buhr, 2008). On the other hand, another RCT included 192 patients with obesity and osteoarthritis, who were treated with a very-low-energy diet (VLED) (415 kcal/d) or a low-energy diet (LED) (810kcal/d) for eight weeks, followed by a 1,200 kcal/d diet for eight weeks (Riecke *et al*., 2010). It was found that patients lost 12% of their initial body weight in both groups, with 60% of patients in both groups experiencing reduced symptoms and improved mobility. In addition, patients enrolled on the Cambridge Weight Plan formula diet (800 kcal/d) were able to achieve a 10 to 12 kg weight loss over eight weeks. This amount of weight loss could prevent type 2 diabetes and improve metabolic control for patients on insulin treatment (Leeds, 2016).

Another RCT was carried out on 60 participants with a BMI >27 kg/m^2 and had plaque psoriasis were recruited from the outpatients clinic in Denmark (Jensen *et al*., 2013). After 16 weeks of LED (800 to 1000 kcal/d) or routine dietary guidance (control group), the mean weight change in the LED and control groups was -15.8 kg and -0.4 kg, respectively. The mean change in the Psoriasis Area and Severity Index (PASI) in the LED group was -2.3 and -0.3 in the control group. The mean difference was -2.0 (95% CI: -4.1 to 0.1; p =0.06), which is not statistically significant. Moreover, Vilar-Gomez *et al*. (2015) found that a modest weight loss (7%-10%) was associated with significant improvements in liver histology in patients with obesity and non-alcoholic steatohepatitis (NASH). However, ≥10% weight loss was a prompt resolution of steatohepatitis and improving fibrosis. Furthermore, Johansson *et al*. (2011) found that with the LED programme, participants

who lost ≥15 kg showed greater improvement in the apnoea-hypopnoea index after 1 year than those who lost 10-14.9 kg (-30 vs. -15, p =0.004), or those who lost less than 10 kg (-30 vs. -15, p =0.008).

Therefore, due to the higher initial BMI and range of comorbidities in the GCWMS, and the clinical benefits of losing ≥10 kg of initial weight, the weight loss target of the GCWMS might need to be reviewed and a higher target set.

3.8 Research strengths and limitations

The main strength of this study is that real-life data were obtained from the NHS, providing the largest weight management service dataset available for a programme targeting participants with severe and complex obesity. In addition, the large sample size, and data such as weight and height were measured by trained dieticians and not self-reported. The mean weight change among all patients referred to the GCWMS was reported, and not only those who completed the programme. Therefore, it was possible to ascertain the benefits from attending the programme of treatment for certain. The threshold that defined programme completion was high when compared with previous studies that used lower thresholds. On the other hand, the higher threshold of 80% to mark programme completion means that the weight lost by the group of participants who completed the programme was likely to be greater. In addition, the research reported the outcomes for completers and non-completers, yielding exact quantification of the achievements of the GCWMS.

It is both a strength and limitation of this research that the included sample was not randomly allocated. However, multiple imputations are not applicable for use in this research as the missing data are not random, which might produce misleading results. Moreover, BOCF was not used, because it was assumed that it could assign unrealistic weight regain to subjects whose weight loss near to the end of the programme is known. Consequently, this study benefits from the use of LOCF to minimise the number of individuals who dropped out from the analysis and to allow the analysis to examine weight loss over time. However, it would underestimate weight loss in the short term and overestimates it in the long term (Jorgensen *et al*., 2014); in addition, it ignores the trajectory of weight loss. Jorgensen *et al*. (2014) randomly allocated 561 individuals to groups receiving an anti-obesity drug or a placebo for 60 weeks and measured the rate of weight loss in each group using different analysis methods. At the end of treatment, participants lost 6.8 kg (SE 0.66), 6.4 kg (SE 0.90) and 1.5 kg (SE 0.28) through LOCF, multiple imputation, and BOCF respectively. The researchers concluded that LOCF is a conservative analysis and had a lower SE than the multiple imputation method.

Whilst using real-life data have massive benefits, its use in this study also caused some problems, resulting in poorly specified information or missing data. Additionally, there was a lack of weight measurement when some referred patients missed some of the treatment sessions; another good source of weights was not readily available. For example,

as GP records are not available for research at this point, if the participant drops out it is not possible to determine what subsequently happened to them. There was no control group, as the results depended on participants joining the programme, which differed from the approach adopted in RCTs. Generally, RCTs provide data that illustrate the efficacy, quality and safety of an intervention as endpoints, rather than real world data describing its effectiveness. This study could therefore provide more realistic answers in normal conditions, in contrast to the highly standardised context of RCTs. The comorbidity data, such as diabetes and hypertension are also potentially unreliable, as while these were highlighted in the referral forms from GPs, no access is permitted to the patients' medical records to confirm this. In addition, the data are limited by the lack of additional information regarding factors such as the change in clinical risk factors (e.g. glycaemic control, blood pressure and lipids) or changes in medication doses. A further limitation is that as long-term weight loss outcomes are not available (no GP data are available), the opportunity to evaluate the maintenance phase would be useful to illustrate the effect of GCWMS over a longer time frame.

3.9 Research implications

The lifestyle phase of the GCWMS programme showed modest results, achieving ≥5kg weight loss in 30.5% of individuals who attended at least 2 sessions. This chapter suggests the lifestyle treatment phase is clinically effective for patients who completed the treatment programme, among whom 46% were successful in losing at least 5 kg. In addition, it showed that greater absolute weight loss is achievable by those with higher starting BMIs, which might indicate that the GCWMS goal of ≥5 kg weight loss might not be sufficient to mitigate risk adequately in patients with BMIs ≥40 kg/m^2. Behavioural change is very important if patients are to complete the programme and ultimately guarantee effective weight management. Therefore, it is necessary to evolve the GCWMS in order to facilitate an improved impact. Some recommendations are needed for GCWMS to improve their service; such as, attracting more men to join the programme, encouraging patients from areas of higher socioeconomic deprivation to opt in, and motivating patients to complete the programme to achieve better results. The lifestyle treatment phase, which includes dietary management, exercise and behavioural interventions, should be considered one of the main treatment plans at GCWMS. Therefore, in the next chapter (Chapter 4), the effectiveness of phase 2 treatment will be evaluated by exploring the effect of different interventions in phase 2 (orlistat, LDL and FWL). Further implications and recommendation for the development of the GCWMS will be discussed in Chapter 7.

Chapter 4: Evaluation of the effectiveness of different interventions in phase 2 of the Glasgow and Clyde Weight Management Service programme

4.1 Chapter summary

In addition to the insufficient evidence concerning the effectiveness of weight management services, there is a dearth of studies evaluating the effectiveness of different interventions for treating individuals with obesity. The objective of this research was to evaluate the effectiveness of these interventions (orlistat, low-calorie diet (LCD) and further lifestyle advice (FWL)) in phase 2 of GCWMS, setting a target of achieving ≥5 kg weight loss, exploring the effects of age, sex, initial weight, BMI and co-morbidities such as diabetes and hypertension. Subjects with BMI ≥30 kg/m^2, and who had attended at least 2 sessions in the lifestyle phase and 2 sessions in phase 2 were included. LOCF and programme completers were reported in terms of mean weight changes with 95% confidence intervals, 5 kg and 5% weight losses at the end of phase 2 based on a starting point of the first clinic visit in the lifestyle phase.

Of the 4,709 individuals who chose to participate in phase 2, 3,262 patients attended 2 sessions or more. Of these 536, 1,043 and 1,683 patients selected orlistat, LCD and FWL, respectively. The majority of the patients were female, from the most deprived quintile, had a BMI between 35 kg/m^2 and 50 kg/m^2, and had neither diabetes nor hypertension. The mean weight change for the participants who opted into the service and attended at least 2 sessions in each phase (the lifestyle phase and phase 2) was -6.56 kg (95% CI: -6.7 to -6.3 kg); and 54.9% of those lost their target weight. The mean weight change at the end of phase 2, starting with the first clinic visit in the lifestyle phase was -3.31 kg (95% CI: -3.7 to -2.9 kg), -2.39 kg (95% CI: -2.6 to -2.1 kg) and -10.17 kg (95% CI: -10.4 to -9.8 kg) for patients who used orlistat, LCD and FWL, respectively. In terms of target weight loss, 31% of all patients on orlistat, 22% on LCD and 83% on FWL lost at least 5 kg. 39.5%, 25.5% and 86.5% of those who were on orlistat, LCD and FWL, respectively and completed the programme lost ≥5 kg from their initial body weight. A greater proportion of patients who completed the programme lost their target weight (≥5 kg), when compared with all patients who opted in or non-completers.

Outcomes from the phase 1 lifestyle stage influenced the selection of the phase 2 intervention. Those who were successful in the lifestyle phase, and who expressed a preference for further lifestyle intervention, had the highest weight loss by end of phase 2. Orlistat and LCD were selected by those failing to lose significant weight with lifestyle change alone, but they did not result in large numbers achieving ≥5 kg weight loss.

Targeting effective interventions at specific populations and increasing the intensity of phase 2 interventions might improve the programme's overall effectiveness.

4.2 Introduction

GCWMS followed the guidelines to treat individuals with obesity known to be eligible for treatment, as stated in Chapter 3 (SIGN 15, 2010; NICE, 2014). Phase 2 treatment is offered to patients who have completed four months of the lifestyle programme. The three choices offered in phase 2 are LCD or orlistat, if a 5 kg weight loss has not been achieved, or FWL (a continuation of the phase 1 programme) if patients have successfully lost ≥5 kg in the lifestyle phase. A 1,200 or a 1,500 calorie plan may be prescribed for patients who offered LCD based on their personalised dietary prescription (PDP), and if they struggle to reach their target weight loss through a low-fat diet or opted for it rather than prescribed diet, then they were treated with orlistat 120 mg, three times a day.

Orlistat (120 mg) is a non-systemically acting lipase inhibitor, which can be taken three times daily to help patients lose extra weight. Patients with obesity at GCWMS can use orlistat for 3 months in phase 2; and their protocols recommended continuing treatments for longer than 3 months if patients have lost at least 5% of their initial body weight when starting the drug treatment. Patients can continue using orlistat throughout the maintenance phase (phase 3) and for up to 12 months if they continue losing weight. If patients gain more than 3 kg during the programme, then the drug should be discontinued. When patients are discharged from the service, but are continuing to use orlistat, then monitoring them becomes the responsibility of their GP. Those with type 2 diabetes might need longer treatment with orlistat, as their weight loss would be expected to be slower (NHS Great Glasgow and Clyde, 2016).

A previous systematic review and meta-analysis of 44 RCTs by Douketis *et al.* (2005) investigated lifestyle, pharmacologic and surgical treatment of weight loss (researched from 1966 to 2003). The main objective was to investigate the absolute weight loss and the proportion of participants who lost ≥5% of initial body weight and the effects of weight loss on cardiovascular risk factors. It showed that the mean weight change after 1 year for 9,953 subjects in 19 studies receiving orlistat in addition to lifestyle change was 6.1±2.0 kg. The mean weight change after 2 years was 7.2±1.6 kg, based on LOCF. The same study concluded that lifestyle treatment provides less than 5 kg weight loss after 2-4 years, and that pharmacotherapy provides 5-10 kg weight loss after 1-2 years.

In Chapter 3, a cohort study of 7,329 patients was conducted to evaluate the effectiveness of lifestyle treatment; it found 30.5% of all patients who attended ≥2 sessions had lost ≥5

kg. While in this study, the effectiveness of phase 2 treatment was evaluated by studying the variation in effectiveness when adding another intervention to lifestyle change. The principal aim of GCWMS is to achieve a reduction of 5 kg or more in patient's weight; there was a lack of evidence concerning the effect of different interventions on weight management services. Therefore, the main objective of this study was to investigate the proportion of patients who lost ≥5 kg starting from the first clinic visit in the lifestyle phase until the end of phase 2 for each group of patients using LCD, orlistat or FWL. One of the aims of this research was to learn which interventions resulted in greater weight loss.

4.3 Materials and methods

4.3.1 Data source

This study used the same data from the GCWMS as that used in the previous study (Chapter 3, page 116) for evaluating the lifestyle phase. Of 7,329 individuals who attended ≥2 sessions in the lifestyle phase, 4,709 patients chose phase 2 by selecting different interventions.

4.3.2 Inclusion and exclusion criteria

The eligible subjects were adults (aged ≥18 years) with a BMI of ≥30 kg/m^2. Of 4,709 individuals, 3,262 patients attended ≥2 sessions in phase 2. For this study, those participants who attended fewer than 2 sessions were excluded and the patients who attended ≥2 sessions in the lifestyle phase and ≥2 sessions in phase 2 were included.

4.3.3 Definition of programme completion

In phase 2, the patients attended 4 monthly sessions over a period of 3 months, and programme completion was defined as attending ≥3 sessions, equal to 80% of the phase 2 sessions. Therefore, weight loss outcomes were reported for those patients who attended seven sessions or more in the lifestyle phase and at least three sessions in phase 2.

4.3.4 Variables definitions

Age was categorised into six groups: 18-29, 30-39, 40-49, 50-59, 60-69 and ≥70 years. BMI was categorised into four groups: (30-34.9 kg/m^2), (35-39.9 kg/m^2), (40-49.9 kg/m^2) and (≥50 kg/m^2). Weight was categorised into five groups: (<75 kg), (75-99 kg), (100-124 kg), (125-149) and (≥150 kg). The data included information about the presence or absence of diabetes and hypertension in addition to SIMD. The presence of hypertension and diabetes was highlighted on the referral form by the referring clinician.

4.3.5 Statistical analysis

All statistical analyses were completed using Stata version 12.1 (Stata Corporation, College Station, Texas, USA). Statistical significance was defined as p <0.05. Mean weight change and 95% CI were reported for the three different interventions used in the

phase 2 treatment. Differences in the means between two groups and across more than two groups were tested using the t-test and ANOVA test, respectively. In addition, 5 kg and 5% weight loss were reported and the effect of age, sex, deprivation quintiles, initial BMI, diabetes and hypertension were explored. For missing data, the last observation carried forward method was applied.

4.4 Results

4.4.1 Baseline characteristics

Figure 4-1 shows that out of the 4,709 participants, 803 patients were offered orlistat, 1,686 patients were offered LCD and 2,220 were offered FWL. 1,447 patients were excluded because they attended fewer than 2 sessions in phase 2. Therefore, 3,262 patients were eligible for inclusion. Of these, 536 (16.4%), 1,043 (32.0%) and 1,683 (51.6%) selected orlistat, LCD and FWL, respectively. LCD and orlistat were recommended for those patients who had not lost ≥5 kg in the lifestyle phase.

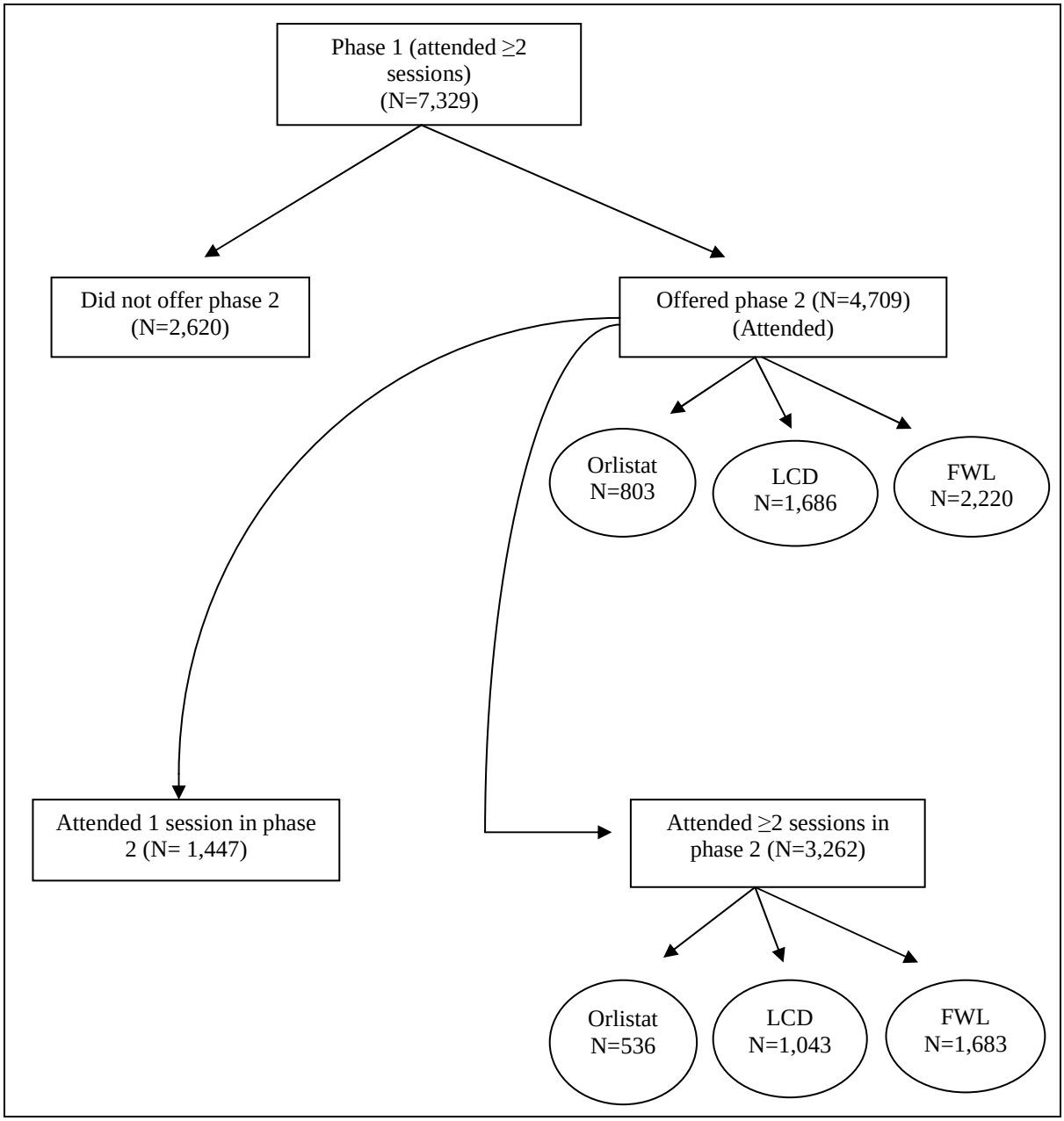

Figure 4-1 Flowchart showing the number of patients who offered phase 2 treatment and their interventions at the GCWMS.

Most of the patients in the first session of phase 2 treatment who selected one of the three different types of interventions were female, from the most deprived quintile. A higher proportion of patients with a BMI between 35 kg/m^2 and 49.9 kg/m^2 and around one fourth and one third of the patients had hypertension and diabetes, respectively **(Table 4-1)**. However, the proportion of female patients who selected orlistat (81.5%) was higher than those who selected LCD (76.7%) or FWL (66.0%). Likewise, the proportion of young participants selecting orlistat in phase 2 was higher than those who selected LCD or FWL. That is, 10.4%, 7.1% and 4.8% of patients (aged 18-29 years) in phase 2 selected orlistat, LCD and FWL, respectively. The proportion of patients from the most deprived quintile who selected orlistat (41.8%) was higher than those who selected LCD (37.0%) or FWL (36.2%). In addition, the percentage of people without diabetes who selected orlistat was greater than that of the two groups who selected LCD or FWL.

Variables	7,329 Lifestyle phase		N=536 (16.4%) Orlistat (≥2 sessions)		N=1,043 (31.9%) LCD (≥2 sessions)		N=1,683 (51.5%) FWL (≥2 sessions)	
Age	N	%	N	%	N	%	N	%
18-29	671	**9.2**	56	**10.4**	74	**7.1**	80	**4.8**
30–39	1,050	**14.3**	107	**20.0**	115	**11.0**	217	**12.9**
40–49	1,821	**24.8**	152	**28.3**	209	**20.0**	403	**23.9**
50–59	1,946	**26.6**	135	**25.2**	286	**27.4**	487	**28.9**
60–69	1,374	**18.7**	69	**12.9**	259	**24.8**	381	**22.6**
≥70	437	**6.0**	15	**2.8**	93	**8.9**	112	**6.7**
Missing	30	**0.4**	2	**0.4**	7	**0.7**	3	**0.2**
Gender								
Males	1,979	**27.0**	98	**18.3**	243	**23.3**	570	**33.9**
Females	5,345	**72.9**	437	**81.5**	800	**76.7**	1,111	**66.0**
Missing	5	**0.1**	1	**0.2**			2	**0.1**
SIMD								
Most deprived	2,966	**40.5**	224	**41.8**	384	**37.0**	610	**36.2**
2	1,410	**19.2**	118	**22.0**	191	**18.3**	351	**20.9**
3	1,099	**15.0**	78	**14.6**	180	**17.2**	250	**14.9**
4	891	**12.2**	57	**10.6**	123	**11.7**	224	**13.3**
Least deprived	924	**12.6**	52	**9.7**	161	**15.4**	238	**14.1**
Not known	39	**0.5**	7	**1.3**	4	**0.4**	10	**0.6**
BMI								
30–34.9	840	**11.5**	46	**8.6**	164	**15.7**	187	**11.1**
35–39.9	2,346	**32.0**	171	**31.9**	318	**30.5**	499	**29.5**
40–49.9	3,197	**43.6**	254	**47.8**	439	**42.1**	736	**43.7**
≥50	946	**12.9**	65	**12.1**	122	**11.7**	261	**15.5**
Weight kg								
<75	44	**0.6**	3	**0.5**	14	**1.3**	4	**0.2**
75–99	1,930	**26.3**	154	**28.7**	331	**31.7**	373	**22.2**
100–124	3,252	**44.4**	241	**45.0**	458	**43.9**	739	**43.9**
125–149	1,558	**21.3**	106	**19.8**	177	**17.0**	411	**24.4**
≥150	545	**7.4**	32	**6.0**	63	**6.0**	156	**9.3**
Diabetes*								
No	5,757	**78.6**	442	**82.5**	755	**72.4**	1,309	**77.8**
Yes	1,572	**21,4**	94	**17.5**	288	**27.6**	374	**22.2**
Hypertension*								
No	6,139	**83.8**	451	**84.2**	860	**82.5**	1,394	**82.8**
Yes	1,190	**16.2**	85	**15.8**	183	**17.5**	289	**17.2**

Table 4-1 Characteristics of patients in phase 2 (LCD: low calorie diet; FWL: further weight loss). (*): Diabetes/Hypertension highlighted on referral form.

4.4.2 Phase 2 selection

Table 4-2 shows the results for the lifestyle weight loss phase, and the patient's selection in phase 2. The mean weight changes at the end of the lifestyle phase for participants who were offered orlistat, LCD or FWL were -1.40 kg (95% CI: -1.6 to -1.1 kg), -1.89 kg (95% CI: -2.0 to -1.7 kg) and -8.27 kg (95% CI: -8.4 to -8.0 kg), respectively. Those who did not select any intervention in phase 2 lost -1.6 kg (95% CI: -1.7 to -1.5 kg) in the lifestyle phase.

Intervention	N	Mean weight change and 95% CI
Orlistat (≥2 sessions)	536	-1.40 (-1.6 to -1.1)
LCD (≥2 sessions)	1,043	-1.89 (-2.0 to -1.7)
FWL (≥2 sessions)	1,683	-8.27 (-8.4 to -8.0)
Never chose phase 2	2,620	-1.6 (-1.7 to -1.5)

Table 4-2 Lifestyle phase outcomes (mean weight change) among different group choices in phase 2 (CI: Confidence interval; N: Number).

4.4.3 Effect of orlistat

4.4.3.1 Weight loss outcomes for all participants and completers for those who selected orlistat in phase 2

Table 4-3 shows that 45.7% (*n* =245) of those patients (*n* =536) who started the GCWMS were considered to have completed the lifestyle phase and phase 2 (orlistat); of those, 39.5% had lost ≥5 kg and their mean weight change was -4.33 kg (95% CI: -4.9 to -3.6 kg). On the other hand, 31% of all patients (completers and non-completers) had lost 5 kg or more and their mean weight change at the end of phase 2 was -3.31 kg (95% CI: -3.7 to -2.9 kg).

Phase 1 + Phase 2 (orlistat)	**N**	**%**	**Mean weight change and 95% CI (kg)**	**Lost ≥5 kg**	**Lost≥5%**
Completers (≥7 p1 and ≥3 p2 sessions)	245	45.7	-4.33 (-4.9 to -3.6)	97 (39.5%)	81 (33%)
Non-completers (<7 p1 and <3 p2 sessions)	291	45.2	-2.45 (-2.9 to -1.9)	69 (24%)	58 (20%)
Total (≥2 sessions)	**536**		-3.31 (-3.7 to -2.9)	166 (31%)	139 (26%)

Table 4-3 Cumulative weight loss at the end of phase 2 (orlistat) from first clinic visit in lifestyle phase (CI: Confidence interval; p1: phase 1; p2: phase 2; N: Number).

4.4.3.2 Mean weight change and target weight loss (5 kg) for subgroup of participants who selected orlistat in phase 2

Table 4-4 shows that out of 536 individuals who were offered orlistat and attended ≥2 sessions, 81.5% were female and 41.8% were from the most deprived quintile. The mean age was 46.5 years and the mean weight and BMI were 113.6 kg and 42.5 kg/m^2, respectively. In total, 82.5% and 84.2% of patients had no diabetes or hypertension, respectively. There was no difference in the proportion of males (30.5%) to females (31%) achieving their target weight loss at the end of phase 2. There was no clear trend between initial BMI or weight and successful weight loss. Men and women aged ≥70 years had more success with weight loss; however, the sample size of these two groups (*n* =2 and *n* =13 respectively) was small. In addition, presence or absence of diabetes or high blood pressure and deprivation did not seem to affect the proportion of patients achieving their target weight loss.

			Total (completers & non-completers)				Completers			
		N	**Mean weight change and 95% CI**	***P*-value**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**	**N (%) of total**	**Mean weight change and 95% CI**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**
All		536	-3.31 (-3.7 to -2.9)		165 (31%)	139 (26%)	245 (45.5)	-4.33 (-4.9 to -3.6)	97 (39.5%)	81 (33%)
Gender	Male	98	-3.33 (-4.3 to -2.3)	0.93	30 (30.5)	19 (19.5)	48 (49)	-4.46 (-5.7 to -3.1)	18 (37.5)	12 (25)
	Female	437	-3.29 (-3.7 to 2.8)		135 (31)	120 (27.5)	196 (45)	-4.28 (-5.0 to -3.5)	78 (40)	69 (35)
	Missing	1					1			
SIMD	1 (most deprived	224	-3.13 (-3.8 to -2.4)		61 (27)	48 (21.5)	111 (49.5)	-4.45 (-5.6 to -3.2)	41 (37)	31 (28)
	2	118	-3.66 (-4.3 to -2.9)		40 (34)	33 (28)	47 (40)	-4.47 (-5.4 to -3.5)	20 (42.5)	16 (34)
	3	78	-3.94 (-4.9 to -2.9)	0.46	33 (42.5)	27 (34.5)	34 (43.5)	-4.73 (-6.1 to -3.3)	16 (47)	15 (44)
	4	57	-2.66 (-3.4 to -1.8)		14 (24.5)	13 (23)	29 (51)	-3.17 (-4.5 to -1.8)	10 (34.5)	9 (31)
	5 (least deprived	52	-3.01 (-4.3 to -1.6)		17 (32.5)	16 (31)	22 (42)	-4.21 (-5.9 to -2.4)	9 (41)	8 (36.5)
	Missing	7					2			
Age	≤29	56	-2.99 (-4.4 to -1.5)		17 (30.5)	14 (25)	24 (43)	-4.97 (-7.1 to -2.7)	10 (41.5)	9 (37.5)
	30-39	107	-2.54 (-3.4 to -1.6)		27 (25)	21 (19.5)	47 (44)	-3.15 (-4.6 to -1.7)	13 (27.5)	10 (21)
	40-49	152	-3.42 (-4.0 to -2.7)		48 (31.5)	38 (25)	70 (46)	-4.44 (-5.4 to -3.4)	31 (44.5)	23 (33)
	50-59	135	-3.83 (-4.7 to -2.8)	0.32	46 (34	39 (29)	65 (48)	-4.79 (-6.4 to -3.1)	26 (40)	22 (34)
	60-69	69	-3.14 (-3.9 to -2.3)		60 (29)	17 (42.5)	30 (43.5)	-4.35 (-5.4 to -3.2)	13 (43.5)	11 (36.5)
	≥70	15	-4.46 (-6.0 to -2.8)		6 (40)	8 (53.5)	8 (53.5)	-4.12 (-5.5 to -2.7)	3 (37.5)	5 (62.5)
	Missing	2					1			
Male	≤29	9	-4.74 (-9.7 to 0.2)		5 (55.5)	3 (33.5)	5 (55.5)	-4.56 (-6.9 to -2.1)	2 (40)	1 (20)
	30-39	18	-3.60 (-6.0 to -1.1)		7 (39)	3 (16.5)	11 (61)	-3.82 (-7.5 to -0.1)	4 (36.5)	2 (18)
	40-49	22	-3.36 (-5.3 to -1.4)	0.79	5 (22.5)	3 (13.5)	7 (32)	-5.69 (-10.8 to -0.5)	3 (43)	2 (28.5)
	50-59	27	-2.69 (-4.4 to -0.9)		6 (22)	5 (18.5)	11 (40.5)	-4.72 (-6.2 to -3.1)	4 (36.5)	3 (27)
	60-69	20	-2.94 (-4.7 to -1.1)		6 (30)	3 (15)	13 (65)	-4.03 (-6.1 to -1.9)	5 (38.5)	3 (23)
	≥70	2	-6.75 (-10.6 to -2.8)		1 (50)	2 (100)	1 (50)	-4.80	0	1 (100)

			Total (completers & non-completers)				Completers			
		N	**Mean weight change and 95% CI**	***P*-value**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**	**N (%) of total**	**Mean weight change and 95% CI**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**
Female	≤29	47	-2.65 (-4.1 to -1.1)	0.13	12 (25.5)	11 (23.5)	19 (40.5)	-5.08 (-7.8 to -2.3)	8 (42)	8 (42)
	30-39	89	-2.32 (-3.2 to -1.3)		20 (22.5)	18 (20)	36 (40.5)	-2.95 (-4.5 to -1.3)	9 (25)	8 (22)
	40-49	129	-3.41 (-4.0 to -2.7)		42 (32.5)	35 (27)	62 (48)	-4.27 (-5.2 to -3.3)	27 (43.5)	21 (34)
	50-59	108	-4.11 (-5.2 to -3.0)		40 (37)	34 (31.5)	54 (50)	-4.81 (-6.7 to -2.8)	22 (40.5)	19 (35)
	60-69	49	-3.23 (-4.1 to -2.2)		14 (28.5)	14 (28.5)	17 (34.5)	-4.60 (-5.8 to -3.3)	8 (47)	8 (47)
	≥70	13	-4.11 (-5.8 to -2.4)		5 (38.5)	6 (46)	7 (54)	-4.02 (-5.6 to -2.4)	3 (43)	4 (57)
	Missing	2								
BMI	30–34.9	46	-3.52 (-4.4 to -2.5)	0.55	14 (30.5)	18 (39)	15 (32.5)	-4.17 (-5.3 to -2.9)	5 (33.5)	9 (60)
	35–39.9	171	-3.16 (-3.7 to -2.5)		56 (32.5)	48 (28)	81 (47.5)	-4.54 (-5.2 to -3.8)	39 (48)	33 (40.5)
	40–49.9	254	-3.53 (-4.1 to -2.8)		79 (31)	63 (25)	116 (45.5)	-4.54 (-5.6 to -3.3)	43 (37)	34 (29.5)
	≥50	65	-2.66 (-3.8 to -1.5)		17 (26)	10 (15.5)	33 (50.5)	-3.1 (-4.5 to -1.6)	10 (30)	5 (15)
Weight	<75	3	-3.26 (-6.9 to 0.4)	0.38	1 (33.5)	1 (33.5)	2 (66.5)	-4.54 (-9.1 to 0.07)	1 (50)	1 (50)
	75–99	154	-3.40 (-3.9 to -2.8)		54 (35)	61 (39.5)	70 (45.5)	-4.43 (-5.2 to -3.6)	34 (48.5)	40 (57)
	100–124	241	-3.06 (-3.6 to -2.5)		68 (28)	50 (20.5)	106 (44)	-3.77 (-4.4 to -3.0)	35 (33)	24 (22.5)
	125–149	106	-4.00 (-5.2 to -2.7)		35 (33)	23 (21.5)	52 (49)	-5.29 (-7.5 to -3.0)	21 (40.5)	13 (25)
	≥150	32	-2.41 (-4.4 to -0.3)		8 (25)	4 (12.5)	15 (47)	-4.38 (-7.3 to -1.3)	6 (40)	3 (20)
Diabetes	No	442	-3.39 (-3.8 to -2.9)	0.40	140 (31.5)	117 (26.5)	200 (45)	-4.38 (-5.1 to -3.6)	81 (40.5)	68 (34)
	Yes	94	-2.93 (-3.8 to -2.0)		26 (27.5)	22 (23.5)	45 (48)	-4.10 (-5.2 to -2.9)	16 (35.5)	13 (29)
Hypertension	No	451	-3.35 (-3.8 to -2.9)	0.62	137 (30.5)	116 (25.5)	203 (45)	-4.28 (-5.0 to -3.5)	75 (37)	64 (31.5)
	Yes	85	-3.07 (-3.9 to -2.2)		28 (33)	22 (26)	41 (48)	-4.52 (-5.5to -3.4)	21 (51)	16 (39)

Table 4-4 Subgroup analyses of weight loss from the lifestyle phase until the end of phase 2 (patients who chose orlistat). *P*-values were determined using t-test and an ANOVA test (p-value <0.05 considered statistically significant) (CI: Confidence interval; N: Number).

4.4.3.3 Weight loss outcomes at the end of lifestyle phase and at the end of phase 2 for the group of patients who selected orlistat

Table 4-5 shows that of the 536 patients still enrolled at the end of phase 2 (orlistat) who had already attended the lifestyle phase, 73.2% lost less than 5 kg in the lifestyle phase and 18.6% gained less than 2.5 kg. Whereas, at the end of phase 2 (phase 1 + orlistat phase), 50.3% had lost less than 5 kg and 10.6% had gained less than 2.5 kg. In terms of target weight loss, 2.5% of the patients lost ≥5 kg at the end of the lifestyle phase, compared with 30.9% at the end of orlistat phase.

	Weight change	**Lifestyle phase (**N=536) N (%)	**Phase 1+2 (**N=536) N (%)
Weight gain	>7.5	4 (0.7)	8 (1.4)
	5 – < 7.5	4 (0.7)	6 (1.1)
	2.5 – < 5.0	21 (3.9)	29 (5.4)
	0 – < 2.5	100 (18.6)	57 (10.6)
Weight loss	0 – > (-2.5)	229 (42.7)	119 (22.2)
	-2.5 – > (-5.0)	164 (30.5)	151 (28.1)
	-5.0 – < (-7.5)	10 (1.8)	101 (18.8)
	> -7.5	4 (0.7)	65 (12.1)

Table 4-5 Weight gain and weight loss in the lifestyle phase, the lifestyle phase + phase 2 for the patients who selected orlistat.

4.4.4 Effect of LCD

4.4.4.1 Weight loss outcomes for all participants and completers who selected LCD in phase 2

Of the 1,043 patients who selected LCD, 51.5% completed the programme; 37% of the patients were from most deprived quintile; 76.7% were female; the mean age was 52.4 years; and the mean weights and BMIs was 111.5 kg and 41.7 kg/m^2, respectively. In addition, 27.6% and 17.5% of the patients had diabetes and hypertension respectively.

At the end of phase 2, of the patients who used LCD, 22% and 18% had lost ≥5 kg and ≥5%, respectively; and the mean weight change was -2.39 kg (95% CI: -2.6 to -2.1 kg). In terms of completing the programme, treatment by attending seven or more sessions in the lifestyle phase and three or more sessions in phase 2, mean weight change was -2.84 kg (95% CI: -3.1 to -2.5 kg); and around 25.5% and 20.5% of completers had lost ≥5 kg and ≥5%, respectively **(Table 4-6)**.

Phase 1 + Phase 2 (LCD)	**N**	**%**	**Mean weight change and 95% CI (kg)**	**Lost ≥5 kg**	**Lost ≥5%**
Completers (≥7 p1 and ≥3 p2 sessions)	538	51.5	-2.84 (-3.1 to -2.5)	137 (25.5%)	111 (20.5%)
Non-completers (<7 p1 and <3 p2 sessions)	505	48.4	-1.91 (-2.3 to -1.4)	91 (18%)	76 (15%)
Total (≥2 sessions)	**1,043**		-2.39 (-2.6 to -2.1)	228 (22%)	188 (18%)

Table 4-6 Cumulative weight loss at end of phase 2 (LCD) from the first clinic visit in the lifestyle phase (CI: Confidence interval; p1: phase 1; p2: phase 2; N: Number).

4.4.4.2 Outcomes for subgroups who selected LCD in phase 2

Table 4-7 shows that young men (aged ≤29 years) were more successful at achieving their target weight loss (33%), whereas a small proportion (16%) of young women (aged ≤29 years) lost ≥5 kg. Deprivation did not affect the proportion losing their target weight. In general, older participants lost significantly more weight than younger ones (p =0.001); and the lighter patients at baseline lost significantly more weight than the heaviest patients (p =0.02). There was no statistically significant difference between people with diabetes and those without diabetes in terms of their weight loss, the mean weight change was -2.26 kg (95% CI: -2.6 to -1.8 kg) and -2.40 kg (95% CI: -2.7 to -2.0 kg); p-value =0.53. In addition, there was no difference between those with and without hypertension in terms of weight loss (p =0.22).

			Total (completers & non-completers)				Completers			
		N	**Mean weight change and 95% CI**	***P*-value**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**	**N (%) of total**	**Mean weight change and 95% CI**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**
All		1,043	-2.39 (-2.6 to -2.1)		228 (22)	188 (18)	538 (51.5)	-2.84 (-3.1 to -2.5)	137 (25.5)	111 (20.5)
Gender	Male	243	-2.41 (-2.8 to -1.9)	0.93	59 (24)	29 (12)	129 (53)	-2.78 (-3.3 to -2.2)	35 (27)	18 (14)
	Female	800	-2.38 (-2.7 to -2.0)		169 (21)	159 (20)	409 (51)	-2.86 (-3.2 to -2.4)	102 (25)	93 (23)
	Missing									
SIMD	1 (most deprived)	384	-2.48 (-3.0 to -1.8)	0.86	98 (25.5)	69 (18)	197 (51)	-2.85 (-3.4 to -2.2)	55 (28)	39 (20)
	2	191	-2.07 (-2.5 to -1.5)		34 (18)	30 (15.5)	96 (50)	-2.35 (-3.0 to -1.6)	19 (20)	15 (15.5)
	3	180	-2.45 (-3.0 to -1.8)		36 (20)	31 (17)	88 (49)	-3.24 (-4.2 to -2.2)	26 (29.5)	23 (26)
	4	123	-2.59 (-3.2 to -1.9)		31 (25)	28 (22.5)	65 (53)	-2.87 (-3.7 to -2.0)	19 (29)	16 (24.5)
	5 (least deprived)	161	-2.31 (-3.0 to -1.5)		29 (18)	30 (18.5)	89 (55)	-2.91 (-3.5 to -2.2)	18 (20)	19 (21)
	Missing	4					3			
Age	≤29	74	-0.34 (-2.5 to 1.8)	0.001	13 (17.5)	10 (13.5)	32 (43)	-2.13 (-4.6 to 0.3)	8 (25)	7 (22)
	30-39	115	-2.68 (-3.6 to -1.6)		26 (22.5)	19 (16.5)	59 (51)	-2.779 (-3.7 to -1.8)	15 (25.5)	10 (17)
	40-49	209	-2.08 (-2.5 to -1.6)		42 (20)	30 (14.5)	101 (48)	-2.67 (-3.3 to -1.9)	26 (25.5)	20 (20)
	50-59	286	-2.23 (-2.7 to -1.7)		59 (20.5)	50 (17.5)	142 (49.5)	-2.09 (-2.7 to -1.4)	28 (19.5)	22 (15.5)
	60-69	259	-3.02 (-3.5 to -2.4)		65 (25)	56 (21.5)	147 (56.5)	-3.60 (-4.1 to -3.0)	42 (28.5)	34 (23)
	≥70	93	-3.08 (-3.6 to -2.5)		23 (24.5)	22 (23.5)	54 (58)	-3.5 (-4.2 to -2.7)	18 (33)	18 (33)
	Missing	7					3			
Male	≤29	6	-3.41 (-6.7 to -0.04)	0.18	2 (33)	1 (16.5)	4 (66.5)	-4.10 (-7.8 to -0.3)	1 (25)	1 (25)
	30-39	19	-2.96 (-3.9 to -1.9)		4 (21)	0	9 (47)	-3.21 (-4.6 to -1.7)	2 (22)	0
	40-49	45	-1.24 (-2.1 to -0.2)		8 (17.5)	2 (4.5)	17 (38)	-1.68 (-3.2 to -0.1)	3 (17.5)	1 (6)
	50-59	69	-2.48 (-3.4 to -1.5)		18 (26)	9 (13)	35 (50.5)	-3.04 (-4.0 to -2.0)	11 (31.5)	4 (11.5)
	60-69	82	-2.81 (-3.4 to -2.1)		22 (27)	13 (16)	48 (58.5)	-2.82 (-3.7 to -1.9)	13 (27)	8 (16.5)
	≥70	17	-2.44 (-4.0 to -0.8)		5 (29.5)	4 (23.5)	14 (82.5)	-2.62 (-4.6 to -0.6)	5 (35.5)	4 (28.5)
	Missing	5					2			

			Total (completers & non-completers)			Completers				
		N	**Mean weight change and 95% CI**	***P*-value**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**	**N (%) of total**	**Mean weight change and 95% CI**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**
Female	≤29	68	-0.07 (-2.4 to 2.3)	0.001	11 (16)	9 (13)	28 (41)	-1.85 (-4.6 to 0.9)	7 (25)	6 (21.5)
	30-39	96	-2.62 (-3.8 to -1.4)		22 (23)	19 (20)	50 (52)	-2.70 (-3.8 to -1.5)	13 (26)	10 (20)
	40-49	164	-2.32 (-2.8 to -1.7)		34 (20.5)	28 (17)	84 (51)	-2.87 (-3.6 to -2.1)	23 (27.5)	19 (22.5)
	50-59	217	-2.15 (-2.7 to -1.5)		41 (19)	41 (19)	107 (49)	-1.79 (-2.6 to -0.9)	17 (16)	18 (17)
	60-69	177	-3.11 (-3.8 to -2.4)		43 (24)	43 (24)	99 (56)	-3.98 (-4.7 to -3.2)	29 (29)	26 (26)
	≥70	76	-3.22 (-3.7 to -2.6)		18 (23.5)	18 (23.5)	40 (52.5)	-3.80 (-4.4 to -3.1)	13 (32.5)	14 (35)
	Missing	2					1			
BMI	30–34.9	164	-2.95 (-3.3 to -2.5)	0.04	37 (22.5)	48 (29)	93 (56.5)	-3.57 (-4.1 to -3.0)	27 (29)	32 (34.5)
	35–39.9	318	-2.40 (-2.8 to -1.9)		70 (22)	68 (21.5)	168 (53)	-2.81 (-3.3 to -2.2)	48 (28.5)	45 (26.5)
	40–49.9	439	-2.39 (-2.7 to -1.9)		93 (21)	58 (13)	220 (50)	-2.84 (-3.3 to -2.3)	49 (22)	28 (12.5)
	≥50	122	-1.35 (-2.9 to 0.2)		29 (23.5)	14 (11.5)	57 (46.5)	-1.74 (-3.3 to -0.1)	14 (24.5)	7 (12)
Weight	<75	14	-3.03 (-4.3 to -1.7)	0.02	3 (21.5)	5 (35.5)	8 (57)	-4.21 (-5.1 to -3.2)	3 (37.5)	4 (50)
	75–99	331	-2.77 (-3.1 to -2.4)		71 (21.5)	91 (27.5)	184 (55.5)	-3.05 (-3.5 to -2.5)	47 (25.5)	56 (30.5)
	100–124	458	-2.41 (-2.8 to -1.9)		93 (20)	66 (14.5)	239 (52)	-2.83 (-3.3 to -2.3)	57 (24)	38 (16)
	125–149	177	-2.18 (-3.1 to -1.1)		47 (26.5)	21 (12)	79 (44.5)	-3.15 (-4.1 to -2.1)	26 (33)	12 (15)
	≥150	63	-0.67 (-2.2 to 0.8)		15 (25)	5 (8)	28 (44.5)	-0.28 (-2.7 to 2.2)	5 (18)	2 (7)
Diabetes	No	755	-2.40 (-2.7 to -2.0)	0.53	174 (23)	145 (19)	390 (51.5)	-2.90 (-3.3 to -2.4)	101 (26)	85 (21.5)
	Yes	288	-2.26 (-2.6 to -1.8)		55 (19)	43 (15)	148 (51.5)	-2.67 (-3.1 to -2.1)	37 (25)	27 (18)
Hypertension	No	860	-2.31 (-2.6 to -1.9)	0.22	190 (22)	157 (18)	431 (50)	-2.84 (-3.2 to -2.4)	115 (26.5)	96 (22)
	Yes	183	-2.77 (-3.3 to -2.2)		39 (21)	31 (17)	107 (58.5)	-2.84 (-3.4 to -2.2)	23 (21.5)	16 (15)

Table 4-7 Subgroup analyses of weight loss from the lifestyle phase up to the end of phase 2 (patients who chose LCD). *P*-values were determined with a t-test and ANOVA test (*p*-value <0.05 considered statistically significant) (CI: Confidence interval; N: Number).

4.4.5 Effect of FWL

4.4.5.1 Weight loss outcomes for all participants and completers who selected FWL in phase 2

Patients who were offered FWL in phase 2 did well to lose weight in the lifestyle phase. At the end of phase 2, out of 1,683 subjects who offered FWL, 62.5% completed the programme and continued to do what had been successful for them in the lifestyle phase. The majority of the patients were females from the most deprived quintile. However, a higher proportion of men and those from the least deprived quintile completed the programme. A higher proportion of men and women aged ≥40 years completed the FWL programme than those aged ≤29 years or 30-39 years. The mean age of patients who selected the FWL was 51.8 years, and men were generally older than the women (mean ages 53.8 and 50.7 years, respectively). Their mean BMIs and weights were 42.8 kg/m^2 and 118.7 kg, respectively. In addition, 22.2% of individuals had diabetes and 17.2% had hypertension.

Among the 1,683 patients offered FWL, 1,394 (83%) lost at least 5 kg and 1,297 (77%) lost ≥5%; and the mean weight change was -10.17 kg (95% CI: -10.4 to -9.8 kg). Furthermore, of the 1,054 individuals who completed the programme, 86.5% lost 5 kg or more and 82% lost ≥5% at the end of phase 2 **(Table 4-8)**.

Phase 1 + Phase 2 (FWL)	N	%	Mean weight change and 95% CI (kg)	Lost ≥5 kg	Lost ≥5%
Completers (≥7 p1 and ≥3 p2 sessions)	1,054	62.6	-11.13 (-11.5 to -10.7)	913 (86.5%)	864 (82%)
Non-completers (<7 p1 and <3 p2 sessions)	629	37.3	-8.56 (-9.0 to -8.1)	479 (76%)	431 (68.5%)
Total (≥2 sessions)	**1,683**		-10.17 (-10.4 to -9.8)	1,394 (83%)	1,297 (77%)

Table 4-8 Cumulative weight loss at the end of phase 2 (FWL) from first clinic visit in the lifestyle phase (CI: Confidence interval).

4.4.5.2 Outcomes for subgroups who selected FWL in phase 2

Table 4-9 shows men lost more weight than women (p =0.001); the heaviest subjects (≥40 kg/m^2) were lost significantly more weight than the other groups, and were among the greatest proportion losing ≥5 kg. Individuals without diabetes lost more weight than people with diabetes, and so the mean weight change was -10.54 kg (95% CI: -10.8 to -10.1 kg; p =0.001). However, there was no difference between those with and without hypertension in terms of weight loss (p =0.90).

			Total (completers & non-completers)				Completers			
		N	**Mean weight change and 95% CI**	***P*-value**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**	**N (%) of total**	**Mean weight change and 95% CI**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**
All		1,683	-10.17 (-10.4 to -9.8)		1394 (83)	1297 (77)	1054 (62.6)	-11.13 (-11.5 to -10.7)	913 (86.5)	864 (82)
Gender	Male	570	-10.97 (-11.5 to -10.3)	0.001	468 (82)	414 (72.5)	368 (64.5)	-11.97 (-12.7 to -11.2)	319 (86.5)	291 (79)
	Female	1111	-9.76 (-10.1 to -9.4)		926 (83)	883 (79.5)	684 (61.5)	-10.68 (-11.1 to -10.2)	594 (87)	573 (83.5)
	Missing	2					2			
SIMD	1 (most deprived)	610	-10.24 (-10.7 to -9.7)	0.74	510 (83)	468 (76.5)	388 (63.5)	-11.33 (-12.0 to -10.6)	339 (87)	320 (82.5)
	2	351	-9.77 (-10.4 to -9.1)		286 (81.5)	262 (74.5)	211 (60)	-10.53 (-11.3 to -9.6)	180 (85)	165 (78)
	3	250	-10.36 (-11.1 to -9.6)		209 (83.5)	195 (78)	154 (61.5)	-11.37 (-12.3 to -10.3)	137 (89)	130 (84.5)
	4	224	-10.42 (-11.2 to -9.5)		190 (85)	180 (80.5)	140 (62.5)	-11.58 (-12.7 to -10.4)	126 (90)	120 (85.5)
	5 (least deprived)	238	-10.23 (11.1 to -9.3)		194 (81)	187 (78)	155 (65)	-10.89 (-11.9 to -9.8)	129 (83)	127 (82)
	Missing	10					6			
Age	≤29	80	-9.20 (-10.5 to -7.8)	0.009	63 (78.5)	58 (72.5)	47 (58.5)	-10.06 (-12.0 to -8.0)	39 (83)	37 (78.5)
	30-39	217	-10.4 (-11.3 to -9.5)		175 (80)	155 (71)	123 (56.5)	-11.52 (-12.7 to -10.3)	105 (85)	96 (78)
	40-49	403	-10.90 (-11.6 to 10.1)		336 (83)	310 (76.5)	262 (65)	-12.02 (-12.9 to -11.1)	224 (85.5)	210 (80)
	50-59	487	-10.06 (-10.6 to -9.4)		398 (81.5)	374 (76.5)	300 (61.5)	-11.24 (-12.0 to -10.4)	258 (86)	245 (81.5)
	60-69	381	-10.14 (-10.7 to -9.5)		331 (87)	310 (81.5)	244 (64)	-10.75 (-11.4 to -10.0)	222 (91)	212 (87)
	≥70	112	-8.44 (-9.2 to -7.5)		90 (80)	89 (79.5)	77 (68.5)	-9.07 (-10.1 to -8.0)	66 (85.5)	65 (84.5)
	Missing	3					1			
Male	≤29	19	-11.16 (-14.4 to -7.8)	0.14	15 (79)	14 (73.5)	11 (58)	-12.52 (-17.4 to -7.6)	9 (82)	9 (82)
	30-39	57	-9.75 (-11.8 to -7.6)		41 (72)	27 (47.5)	28 (49)	-11.15 (-14.2 to -8.0)	21 (75)	15 (53.5)
	40-49	109	-12.26 (-13.8 to -10.6)		90 (82.5)	79 (72.5)	69 (63)	-13.35 (-15.3 to -11.3)	58 (84)	54 (78)
	50-59	188	-10.92 (-12.0 to -9.8)		153 (81)	139 (73.5)	117 (62)	-12.42 (-13.8 to -11.0)	102 (87)	93 (79.5)
	60-69	157	-11.12 (-12.2 to -10.0)		136 (86.5)	124 (79)	114 (72.5)	-11.55 (-12.7 to -10.3)	105 (92)	97 (85)
	≥70	39	-8.69 (-10.4 to -6.9)		32 (82)	30 (77)	29 (74.5)	-9.08 (-11.1 to -7.0)	24 (82.5)	23 (79)
	Missing	1								

			Total (completers & non-completers)				Completers			
		N	**Mean weight change and 95% CI**	***P*-value**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**	**N (%) of total**	**Mean weight change and 95% CI**	**Lost ≥5 kg N (%)**	**Lost ≥5% N (%)**
Female	≤29	61	-8.59 (-10.0 to -7.1)	0.009	48 (78.5)	44 (72)	36 (59)	-9.30 (-11.4 to -7.2)	30 (83)	28 (78)
	30-39	160	-10.67 (-11.6 to -9.6)		134 (83)	128 (79.5)	95 (59.5)	-11.63 (-12.9 to -10.3)	84 (88.5)	81 (85)
	40-49	293	-10.40 (-11.1 to -9.6)		245 (83)	230 (78)	192 (65.5)	-11.54 (-12.5 to -10.5)	165 (86)	155 (80.5)
	50-59	298	-9.47 (-10.0 to -8.8)		244 (82)	234 (78.5)	182 (61)	-10.42 (-11.2 to -9.5)	155 (85)	151 (83)
	60-69	224	-9.46 (-10.0 to -8.8)		195 (87)	186 (83)	130 (58)	-10.06 (-10.8 to -9.2)	117 (90)	115 (88.5)
	≥70	73	-8.30 (-9.2 to -7.3)		58 (79.5)	59 (81)	48 (65.5)	-9.06 (-10.1 to -7.9)	42 (87.5)	42 (87.5)
	Missing	2					1			
BMI	30–34.9	187	-8.16 (-8.8 to -7.4)	0.001	141 (75.5)	141 (75.5)	114 (61)	-9.17 (-10.0 to -8.3)	94 (82.5)	95 (83)
	35–39.9	499	-9.31 (-9.8 to -8.8)		413 (82.5)	410 (82)	311 (62)	-10.23 (-10.8 to -9.5)	272 (87.5)	270 (87)
	40–49.9	736	-10.57 (-11.0 to -10.0)		620 (84)	560 (76)	474 (64.5)	-11.61 (-12.2 to -10.9)	413 (87)	383 (81)
	≥50	261	-12.16 (-13.1 to -11.2)		222 (85)	188 (72)	155 (59.5)	-12.99 (-14.2 to -11.7)	136 (87.5)	118 (76)
Weight	<75	4	-5.65 (-7.7 to -3.5)	0.001	3 (75)	3 (75)	2 (50)	-6.75 (-6.8 to -6.6)	2 (100)	2 (100)
	75–99	373	-8.31 (-8.7 to -7.8)		296 (79)	309 (82.5)	216 (58)	-8.80 (-9.3 to -8.2)	179 (83)	188 (87)
	100–124	739	-9.78 (-10.2 to -9.3)		615 (83)	581 (78.5)	473 (64)	-10.91 (-11.4 to -10.3)	417 (88)	399 (84.5)
	125–149	411	-11.20 (-11.9 to -10.4)		342 (83)	291 (70.5)	264 (64)	-12.50 (-13.4 to -11.5)	227 (86)	202 (76.5)
	≥150	156	-13.94 (-15.3 to -12.5)		140 (89.5)	115 (73.5)	99 (63.5)	-13.80 (-15.4 to -12.1)	90 (91)	75 (75.5)
Diabetes	No	1,309	-10.54 (-10.8 to -10.1)	0.001	1102 (84)	1022 (78)	819 (62.5)	-11.51 (-11.9 to -11.0)	713 (87)	673 (82)
	Yes	374	-8.92 (-9.5 to -8.3)		294 (78.5)	277 (74)	235 (63)	-9.85 (-10.5 to -9.1)	202 (86)	193 (82)
Hypertension	No	1,394	-10.17 (-10.5 to -9.8)	0.90	1,157 (83)	1,080 (77.5)	879 (63)	-11.17 (-11.6 to -10.7)	760 (86.5)	722 (82)
	Yes	289	-10.22 (-10.9 to -9.5)		239 (82.5)	219 (75.5)	175 (60.5)	-11.0 (-11.9 to -10.1)	155 (88.5)	144 (82)

Table 4-9 Subgroup analyses of weight loss from the lifestyle phase up to the end of phase 2 (patients who choose FWL). *P*-values were determined using a t-test and ANOVA test (*p*-value <0.05 considered statistically significant) (CI: Confidence interval; N: Number).

4.4.6 Cumulative effects of different phases - entry to phase 2 of the programme depended on the lifestyle phase weight loss

To explore the difference between the effects of the lifestyle phase and the different interventions in phase 2, those who selected orlistat, LCD and FWL were divided into 3 groups (tertiles) based on mean weight change (**Figure 4-2)**. Overall, the majority of the patients in the FWL group lost more weight in the lifestyle phase and continued to lose weight in phase 2. Those who selected FWL and LCD lost most of their weight in the lifestyle phase compared with phase 2. Conversely, orlistat intervention showed a notably positive effect for the group of patients who gained weight in the lifestyle phase, or who lost a small amount of weight in the lifestyle phase. Unfortunately, the group of participants who completed the first 2 phases and selected the LCD did not achieve their weight loss targets. It is important to consider the intensity and duration of phase 2 treatment.

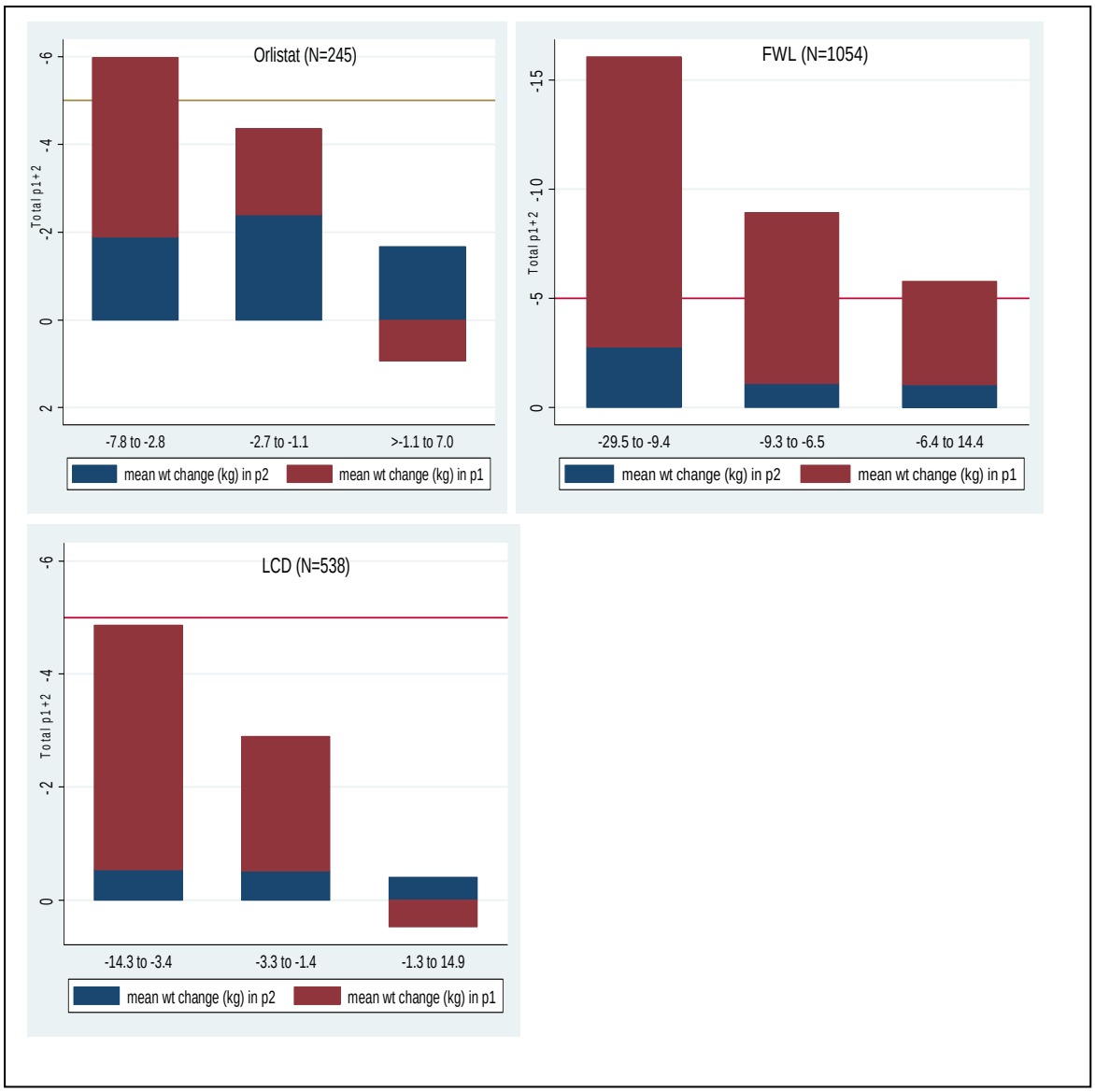

Figure 4-2 The cumulative mean weight change for patients who used different types of interventions and completed the programme categorised by tertile weight change. (A) orlistat (*n* =245), (B) FWL (*n* =1,054) and (C) LCD (*n* =538) (wt: weight; p1: phase 1; p2: phase 2).

4.4.7 Overall outcomes at the end of phase 2

Of 3,262 patients enrolled within the GCWMS who attended phase 2 through the lifestyle phase, 54.9% lost at least 5 kg and 49.7% lost ≥5% of their initial weight at the beginning of the lifestyle phase. The mean weight change was -6.56 kg (95% CI: -6.7 to -6.3 kg). The maximum weight loss was achieved by patients who selected FWL as 83% of them lost at least 5 kg of weight compared with 31% and 22% of those who selected orlistat and LCD, respectively **(Table 4-10)**.

Intervention	N	%	Mean weight change and 95% CI (kg)	Lost ≥5 kg	Lost ≥5%
Orlistat (≥2 sessions)	536	16.4	-3.31 (-3.7 to -2.9)	166 (31%)	139 (26%)
LCD (≥2 sessions)	1,043	32.0	-2.39 (-2.6 to -2.1)	228 (22%)	188 (18%)
FWL (≥2 sessions)	1,683	51.6	-10.17 (-10.4 to -9.8)	1,394 (83%)	1,297 (77%)
Overall at the end of phase 2	**3,262**		-6.56 (-6.7 to -6.3)	1,793 (54.9%)	1,623 (49.7%)

Table 4-10 Total lifestyle phase + phase 2 outcomes and weight change among groups of patients who selected different interventions (CI: Confidence interval; N: Number).

4.5 Summary of the main findings

- 44.5% of those patients who attended the lifestyle phase went on to attend phase 2.
- Those patients who did well (lost ≥5 kg) in the lifestyle phase were offered FWL in phase 2.
- The majority of the patients participating in the three different interventions lost most of the weight in the lifestyle phase. However, in terms of completion, those who were on orlistat reached their weight loss target in phase 2, although just 2.5% had lost ≥5 kg in the lifestyle phase.
- There was no difference in weight loss outcomes according to sex, SIMD, age, initial BMI, and presence or absence of diabetes and hypertension in the weight loss of the orlistat group.
- There was a variation between initial BMI and mean weight change for those on LCD and FWL (i.e. the mean weight loss was higher in the lighter participants on LCD and higher in heaviest people on FWL).
- Patients who did well in the lifestyle phase continued to lose weight in phase 2.
- Those on LCD experienced a smaller amount of weight loss than the patients on FLW or orlistat interventions.

4.6 Discussion

This study set out to assess the impact of different interventions on weight loss, such as FWL, LCD and orlistat, by reporting weight change outcomes at the end of the second phase of a NHS weight management programme (phase 2). The research demonstrated that NHS GCWMS achieved a 5 kg weight loss in 54.9% of the participants who attended at least 2 sessions in phase 2 when the LOCF analysis was used. This equated to 49.7% of patients losing 5% of their body weight. 83% of those selecting FWL lost at least 5 kg at the end of phase 2, compared with 31% and 22% of participants selecting orlistat and LCD, respectively. Therefore, 77% of patients selecting FWL, 26% selecting orlistat, and 18% of patients selecting LCD lost 5% of their body weight.

4.6.1 Opt in and baseline characteristics

The results reported in this chapter outline the effectiveness of the different interventions offered for patients in the phase 2 treatment of the larger weight management programme. The mean BMIs for those participants offered orlistat and LCD was lighter than the participants who offered the FWL intervention, indicating that they might have been heavier when starting the lifestyle phase. SIGN guidelines stated that the most effective first line for the prevention and management of obesity is dietary and lifestyle intervention (SIGN 115, 2010). In total, 45.5% of participants completing the lifestyle phase dropped out and did not complete the weight management programme. The reason for this is unknown, although it might be that the patients had achieved the desired weight loss and felt that they no longer needed the service, or possibly it indicated a lack of success and weights regain (Logue *et al*., 2014). Other factors might include health-related problems, lack of motivation and disappointment.

Of the participants included in phase 2, 51.5% selected FWL, based on success losing weight during the lifestyle phase. In general, a higher proportion of patients from the most deprived quintile, females and those with a BMI between 40 and 49.9 kg/m^2 continued to opt in to phase 2; however, men, those in least deprived area, older individuals and patients with higher BMIs had low dropout rates. The suggested reasons for the higher dropout rate in younger patients are, as mentioned in the previous chapter, the priority given to work and to caring for children, and the lack of transportation for those in the most deprived areas, which might lead them to leave the programme. Those with higher BMIs had lower dropout rates, which might be due to concern about their health. 44% of patients included

in phase 2 had a BMI ≥40 kg/m^2, and currently the goal of GCWMS is to achieve 5 kg weight loss. Hence, the GCWMS goal of >5 kg weight loss might not be sufficient to ensure functional improvement in patients with BMI >40 kg/m^2 as it falls short of the target of 10-15% weight loss set by SIGN guidelines.

4.6.2 Weight loss outcomes and comparisons with other weight management programmes

To the best of our knowledge, this is the first study to evaluate the effectiveness of each intervention in a real-life weight management programme; whereas, previous studies evaluated a single intervention or programme phases, regardless of the types of interventions.

A tier 3 service of the Fakenham programme (FWMS) reported that 44.1% of all participants and 53.8% of completers lost ≥5% of initial weight after six months (Jennings *et al*., 2014) (full details in page 70). FWMS offers a lifestyle change for participants to help them achieve their target weight loss over one year. The patients were considered for treatment with orlistat, LELDs or bariatric surgery if they met the clinical criteria. During the period of study, just 36 participants were prescribed orlistat due to a national shortage of the drug; 9 patients were prescribed LELDs. As this study did not report the results for each intervention, it is not possible to compare the results of phase 2 of the GCWMS with FWMS. There are no other tier 3 service providers that have published the outcomes of each intervention.

4.6.2.1 Orlistat

Orlistat (360 mg/day) users in phase 2 had completed the lifestyle intervention in phase 1. Mean weight loss improved (-1.9 kg) for all 536 participants using orlistat, compared with the same group of participants (-1.4 kg) in the lifestyle phase. In the HTA journal, a previous systematic review of eight RCTs by Avenell *et al*. (2004) stated that the addition of orlistat to the diet was accompanied by weight loss at 12 months; the mean difference in weight between orlistat plus diet versus placebo plus diet was -3.01 kg (95% CI: -3.48 to -2.54 kg). This suggests that using orlistat after the issuance of dietary advice can improve long-term weight loss.

While several RCTs have studied the effect of orlistat on weight loss, the majority of them reported the effects on patients who spent at least a year using the drug. A RCT was undertaken to assess the efficacy of orlistat to promote weight loss in patients with a BMI 28-47 kg/m^2 over 2-years duration (Sjostrom *et al*., 1998). In total, 743 participants from 15 European centres entered four-week single blind, hypocaloric diet, and then were assigned to orlistat 360 mg or placebo. At the end of the first year, the mean weight change for the orlistat and placebo groups was -10.3 kg and -6.1 kg, respectively. Moreover, the mean weight loss at the end of the first 3 months for the orlistat and placebo group was -7.2 kg and -5.2 kg, respectively.

Another one-year RCT compared the effect of orlistat 360 mg versus placebo on cardiovascular disease in 339 participants with BMIs between 30 and 50 kg/m^2 from 8 centres in Australia and New Zealand. The mean weight loss at a one-year duration for those who used orlistat in conjunction with a lifestyle change was -4.7 kg (Swinburn *et al*., 2005). Additionally, based on the HTA programme, a previous RCT by Micic *et al.* (1999) reviewed the clinical effectiveness of orlistat in the treatment of obesity over 6 months duration. This tested 119 patients with BMI ≥30 kg/m^2 recruited for a two-week diet and then randomised to receive orlistat 360 mg or a placebo. The mean weight change in the orlistat group was -10.7 kg compared with -7.3 kg in the placebo group (O'Meara *et al*., 2001). A prospective randomised study was carried out to evaluate the efficacy and safety of orlistat 360 mg in 80 patients with obesity (BMI ≥30 kg/m^2) at an outpatient department in India over a 24 week duration. The mean weight change reported was -1.59 kg, -4.65 kg and -5.25 kg at 8 weeks, 16 weeks and 24 weeks, respectively (Jain *et al*., 2011).

A cohort trial, based on real life data, assessed the effect of orlistat on body weight over 3 years, when delivered in a primary care setting in a UK population. Mean BMI in that study was 37.2 kg/m^2, and the weight change in the first 4 months for all 99,420 participants was -0.94 kg/month (95% CI: -0.93 to -0.95 kg/month), meaning the patients lost 2.82 kg after 3 months duration (Douglas *et al*., 2015).

The SIGN guidelines and United States guidelines recommend orlistat for patients with BMI ≥30 kg/m^2 or 28 kg/m^2 plus comorbidity, who have not achieved their target weight loss through lifestyle intervention. However, based on the above results, the evidence for the effectiveness of orlistat on obesity depends on the results of RCTs, and it is not known how the efficacy measures in the trials relate to effectiveness in the general population. In

conclusion, orlistat was approved for obesity treatment based on its positive benefits as established in RCTs; however, in real life, orlistat is associated with a lesser effect on weight loss than in RCTs (Douglas *et al*., 2015). The current study showed a lower level of weight loss (-3.31 kg within 3 months) than that achieved in RCTs (-7.2 kg at the end of 3 months).

For the subgroup of participants with type 2 diabetes, the current results of the effect of orlistat in real life on weight loss (-2.93 kg (95% CI: -3.8 to -2.0 kg) at 3 months) was less than the weight loss observed in the systematic review and meta-analysis of the RCT (-3.67 kg (95% CI: -4.30 to -3.04 kg) at 3 months) (page 90). In the LOOK AHEAD study, of the 722 individuals who lost less than 5% (at 6 months) of their initial weight after an ILI, 291 patients took orlistat for 6 months and lost an additional 1.8% of their weight (Wadden *et al*., 2009); a result comparable to GCWMS. This may be because the patients in the GCWMS and the LOOK AHEAD study had first gone through the lifestyle intervention phase and then used orlistat; while the participants in the RCTs underwent lifestyle interventions and took orlistat at the same time. Therefore, the latter may have been on a low-fat diet following the lifestyle intervention and certain fats may need to be present in the diet for orlistat to have effect.

Due to the unpleasant side effects of orlistat, such as oily stools, patients may stop taking this medication. A longitudinal study undertaken by Hollywood and Ogden (2011) recruited 566 individuals who was prescribed orlistat by their GP and were registered on the Xenical support system. These patients completed a baseline questionnaire within the first three months of starting the treatment and filled up a follow-up questionnaire after six months. Patients who stopped taking the medication by six months, those who continued taking the medication and those who reported flexible adherence based on their diet were grouped as non-adherers, adherers and lifestyle adherers, respectively. The researchers found that within six months, 47.5%, 30.4% and 22.1% could be classified as non-adherers, adherers and lifestyle adherers, respectively. Therefore, it is recommended that clinicians should not focus only on advising patients about the consequences of eating a high fat diet, but should also promote healthy dietary changes and inform patients about the effectiveness of this kind of medication on weight management. Also, it is important that health care professionals, GPs, patients, and policy makers understand the possible effects of orlistat use as part of the protocol in routine weight management services.

4.6.2.2 LCD

To date, a number of trials appear to have suggested that LCD (800-1800 kcal/day) is associated with modest weight loss (5-6%) at 12 months duration. A previous systematic review and meta-analysis of 80 RCTs after ≥1-year follow-up by (Franz *et al*., 2007) reported weight loss at 6, 12, 24, 36, and 48 months for different interventions. The intervention for 51 studies was diet alone, and the mean weight losses at 6, 12, 24, and 48 months was -4.9, -4.6, -4.4, and -3.0 kg, respectively. Moreover, a previous RCT, performed in three hospitals in the Netherlands and two hospitals in Poland reported a weight change at 12, 24 and 36 months of female patients with obesity and breast cancer. The mean weight difference between the treatment group and the control group at 12 months was -6.2 kg (95% CI: -9.0 to -3.4 kg); however, the sample size for the study was small, reflecting the wide confidence interval (De Waard *et al*., 1993). Additionally, a recent RCT was conducted in the Netherlands on 57 participants with BMI =28-35 kg/m^2 with no comorbidities randomised to a LCD (1,250 kcal/day) for 12 weeks. It found the mean weight change was -8.2 kg (Vink *et al*., 2016); whereas, the mean weight change in the current study for a group of participants (*n* =1,043) selecting LCD (600 kcal deficit diet) was -2.39 kg. However, the aforementioned trial suffered from a small sample size in contrast with the current research and different methodological used.

In the lifestyle phase, LCD was selected by the patients; however, in phase 2, a prescribed LCD was offered to the patients, giving a daily meal plan. The participants in the current study were recruited for lifestyle interventions for 4 months prior to the selected LCD, and they had lost -1.89 kg (95% CI: -2.0 to -1.7 kg). This might reflect the fact that this group of participants were less motivated to lose weight. Furthermore, some of the participants suffered from diabetes, which may have caused more modest weight loss, as it is known that people with type 2 diabetes lose less weight than those without diabetes (Stanford *et al*., 2012). Based on the above and the intensity of the programme (monthly follow up), those who selected LCD as part of a routine weight management programme were less likely to lose weight compared to those in RCTs. Although, in GCWMS, this was effectively rescue therapy; i.e. giving prescribed LCD to those who had failed to lose weight.

A RCT undertaken by Jakicic *et al*. (2012) was conducted with 363 individuals who were overweight or obese with a BMI in the range of 25-40 kg/m^2. Of these individuals, 198 were allocated randomly to a stepped-care weight loss intervention (STEP), while 165

were allocated randomly to a standard behavioural weight loss intervention (SBWI). Although the intervention combining physical exercise, a hypocaloric diet and counselling on a week or month basis for a year and a half was applied to participants in both groups, the programme was fixed in the case of the SBWI group, while the programme could be adjusted according to weight reduction goals in the case of the STEP group. The results revealed that, upon completion of the year-and-a-half programme, the SBWI group achieved a higher average weight reduction than the STEP group, with an average weight difference of -1.3 kg (95% CI: -2.8 to 0.2 kg). The weight percentage decreased by -8.1% (95% CI: -9.4% to -6.9%, p <0.001) and -6.9% (95% CI: -8.0% to -5.8%, p <0.001) in the SBWI group and the STEP group, respectively. However, the real interest is in the rate of success of the intensification of the programme; despite 5 steps to intesify the programme including phone counselling and liquid meal replacements, only 5% of the participants moved back to the target weight loss trajectory during the study. Therefore, it could be concluded that rescue interventions may not work.

With regard to the difference between men and women in terms of weight loss, a previous study by Wamsteker *et al*. (2005) recruited 66 participants with obesity (48 women and 18 men) to be treated in an outpatient clinic in the Netherlands from September 2000 to June 2001 for 8 weeks. They were treated by LCD (800-1000 kcal/day) with meal replacement and the mean weight change was 10.2%. Moreover, there was no significant difference between men and women in terms of percentage weight loss, which concurs with the current research finding (-2.41 kg (95% CI: -2.8 to -1.9 kg) in men and -2.38 kg (95% CI: -2.7 to -2.0 kg) in women).

4.6.2.3 FWL

The current study shows that participants who did well in the lifestyle phase were offered FWL and continued to lose weight in phase 2, but their weight loss in this phase was not considerable (-1.9 kg) compared with (-8.27 kg) in the lifestyle phase. The possible reasons might be the higher number of sessions in the lifestyle phase (fortnightly) compared with phase 2 (monthly). However, this group of participants were still more motivated to lose weight than those who selected orlistat or LCD, as 83% had lost at least 5 kg weight by the end of the lifestyle phase. After that, weight loss plateauing might be expected at the end of phase 2, and patients may experience some difficulties in losing weight. An example from the systematic review and meta-analysis of long term RCTs, found weight loss starts to plateau across all interventions after 6 months. For example, when adding exercise to LCD,

this resulted in a mean weight loss of -7.9 kg at 6 months, then plateaus at -6.7 kg at 12 months (Franz *et al*., 2007). Unfortunately, the data did not explain the reasons why those who were selected for the FWL lost more weight in the lifestyle phase when compared with those in the LCD and orlistat group in phase 2. Behaviour and psychological effects may be suggested as possible reasons for this. In addition, it could be that the members in the group selected for the FWL were heavier (mean BMI was 42.8 kg/m^2), more motivated and more likely to be male (33.9%) than the members of the groups who were offered orlistat or LCD.

4.6.3 Completion and weight loss outcomes for subgroups

Among those participants offered FWL and who completed the lifestyle phase and phase 2 of the programme, 86.5% lost their target weight (≥5 kg); demonstrating they had met their target and achieved further meaningful weight loss (95% CI: -11.5 to -10.7 kg). Overall, the patients who completed the programme by attending ≥7 sessions in the lifestyle phase and ≥2 sessions in phase 2 lost more weight than the non-completers; however, a minority of people who used orlistat or LCD also lost their target weight. This might be due to the higher threshold for completion applied, and the assumption that attendance is directly correlated with weight loss. 45.2%, 48.4% and 37.3% of the patients offered orlistat, LCD, and FWL respectively, did not complete the requisite number of sessions. This might be because they did not reach their weight loss target, or due to the limited choices of appointment times and the service design.

The findings showed that the patients without diabetes lost more weight than patients with diabetes when selecting FWL in phase 2; this is likely to be due to differences in dietary adherence, as suggested in the previous chapter, or might be because most of the patients were using anti-diabetic drugs, a common side-effect of which is weight gain. In addition, patients with diabetes might suffer from other complications, such as neuropathy, foot ulcers or heart disease. Therefore, increasing physical activity, which is an important aspect of the treatment of patients with obesity, is usually unsuccessful. However, there was no difference between the weight losses of people with and without diabetes offered orlistat or LCD, possibly because those with diabetes were successful at remembering to take the orlistat tablet with their anti-diabetic medication. This research and that in the previous chapter explored the effects of gender, SIMD, age and initial BMI on weight change. A previous study by Stubbs *et al*. (2011) reviewed the rate and extent of weight loss in a primary care/commercial weight management partnership system of 34,271

participants referred to Slimming World; it was found that regardless of sex, age and initial weight, if a patient is able to complete a programme of treatment and is encouraged to achieve reasonable weight loss in the first week, they will be likely to succeed in achieving their target weight loss.

4.6.4 Early weight loss prediction

It was found that many more patients achieved their target weight loss in the lifestyle phase than in phase 2, for each of the different interventions. This may be because the lifestyle phase was more effective than phase 2. Another possible explanation could be that weight loss begins quickly then starts to slow naturally (Stubbs *et al*., 2011). In total, 83% of the patients selecting FWL had lost their target (≥5 kg) at the end of the phase 2 treatment. In this group of patients, most weight was lost initially in the lifestyle phase, which indicated that early weight loss was a strong predictor of successful and long-term weight loss. This might be because early weight loss was a sign that the participants were more motivated. Additionally, the Look AHEAD trial included 2,327 participants with type 2 diabetes in the intensive lifestyle intervention (ILI); as individuals who had not achieved ≥2% weight loss within one month were 5.6 (95% CI: 4.5, 7.0) times more likelihood of not achieving 10% or more weight loss within one year (Unick *et al*., 2014).

Further analysis was performed for 2,290 Look AHEAD participants, to test the relationship between the first two months of weight loss and weight 8 years later. It was found that those who achieved ≥2% weight loss in the first month or ≥6% at second month were more likely to achieve a clinically significant weight loss by year 8 (Unick *et al*., 2015). Another study by Jebb *et al*. (2011) reported that during commercial programmes, most weight is lost over 2 months and loss levels off over the following 12 months. The current findings show that initial body weight positively influences the rate of weight loss, which is in agreement with a previous systematic review by Finkler *et al*. (2012). This review examined the factors that might impact the rate of weight loss, and included 35 studies published between January 1995 and December 2009. The same review also found that age was a significant factor in predicting the rate of weight loss with diet, which is consistent with the current research, in which older participants lost more weight compared to younger individuals. This might be because compliance improved in older adults more than in younger adults, or because of the patients' higher level of concern about their health.

4.6.5 Attrition rate

A previous *Lancet* study by Jebb *et al*. (2011) found that the attrition rates in commercial weight loss programmes or in routine clinical practice appear to be highest in the UK (64%), compared with Australia (41%) and Germany (25%). This is probably because of difficulties ensuring flexible appointments for participants or possibly due to a lack of success (Holzapfel *et al*., 2014). This study and the previous literature suggested a correlation between attendance and weight loss. Unfortunately, it is not possible to explore the attrition rate comparative to the amount of weight lost, as there was no information about the weight status of those who did not attend. Similarly, both attrition and weight loss are time-dependent, so it is not easy to establish whether the association between a short duration of attendance and poorer weight loss is causal. Overall, 45.2%, 48.4% and 37.3% of the participants on orlistat, LCD and FWL respectively, dropped out and did not complete their sessions. Hence, there was a higher attrition rate in the LCD and orlistat groups compared with those on FWL; the reasons for this may be due to the challenge of adhering to a very LCD, or not meeting weight loss targets and/or dissatisfaction with the side effects of orlistat.

It is not possible to compare the attrition rate at the end of phase 2 of the GCWMS with other tier 2 services as the results of each intervention were not reported by other services. However, the attrition rate at the end of the lifestyle phase of the GCWMS can be compared with other tier 2 programmes: in the Counterweight programme, attrition was 52.4% at 3 months, 70% at 6 months and 77.5% at 12 months (Laws, 2004); in a study of Weight Watchers' attendees, 44% of participants dropped out after 3 months and did not complete the programme (Ahern *et al*., 2011); the attrition rate over three months in the Rosemary Conley and Slimming World was 55.2% and 64%, respectively. Another study by Hickson *et al*. (2009) reported a high dropout rate for patients who attended an intensive weight management clinic (IWMC) or standard dietetic care in the UK and had a BMI $\geq$32 kg/m^2. Over six months, participants attended lifestyle intervention sessions, 45% attended the IWMC and 55% the standard care. However, of these, only 53% and 19% respectively completed the programme. Unfortunately, the reasons for the high drop-out rate in that study were not investigated; however, it has been suggested that it is important to identify motivated patients.

With respect to the tier 3 programmes, the total dropout rate at the end of the lifestyle phase of the GCWMS (4 months) was 44.8%, compared with 14.3% in the FWMS (within

6 months) (Jennings *et al*., 2014). This striking difference might be due to the different choices of appointment times in primary care, or may have been influenced by the fact that the individuals attending the FWMS programme were motivated by the fact that attendance could help them qualify for a bariatric surgery referral. Attrition rate is not comparable in different weight management programmes due to the differences in the treatment programme setting. Encouraging support from a healthcare provider is aimed at motivating participants to complete the programme treatment, in order to reduce dropout rates, but underlying factors such as location and timing of appointment should be considered.

4.7 Research strengths and limitations

As stated in the previous chapter, this research benefited from access to a diverse-socio-economic population and a large sample size, in the form of the GCWMS data set. This assisted in evaluation of the effectiveness of the lifestyle phase and phase 2, and furthered understanding of diverse individuals' challenges to control their weight. The data used in this research were extracted from a large NHS weight management service providing a real-life follow-up cohort study. A key strength of the present study was that the effectiveness of each intervention in phase 2 was evaluated separately, to determine the effectiveness of the interventions relative to lifestyle change to achieve target of weight loss. A specific strength of the study was that the outcomes of all patients referred to GCWMS were reported, rather than only the outcomes of those who completed the programme. It was observed that attendance is associated with weight loss; therefore, a higher threshold was used to define programme completion. There was no selection bias, as the data pertaining to all participants referred to the GCWMS were included in the study. In addition, the findings were high quality, as the measurements were objective and not self-reported.

This analysis of real-life clinical data is by no means considered definitive in this area, and the limitations affecting the available data make it impossible to conduct a full exploration of all explanatory variables. A number of additional analyses exploring sex, age, initial BMI and socioeconomic status have already been added. Further complicating the study method and previous research through the addition of multivariate models lacking key variables would not alter the clinical message or provide further meaningful insights into this complex area. The major limitations in this study are lack of data because some patients missed their treatment sessions, and because some patients did not complete the programme of treatment.

It was estimated that around 45%, 48% and 37% of the individuals offered orlistat, LCD and FWL, respectively did not complete the treatment programme. There was no information given about those who were never referred to the GCWMS, and it was unfortunate that the data did not include information about why the patients did not complete the programme of treatment. The study only detected cumulative weight loss over a 3 months' duration, plus 4 months of treatment in the lifestyle phase, but did not report weight loss in phase 3 over 12 months, which is termed weight maintenance. NICE (2014) recommends that in terms of weight management interventions outcomes after

twelve months of results are crucial. Therefore, further research should be undertaken to investigate the effectiveness of the maintenance programme (phase 3).

4.8 Research implications

This study confirmed that the patients who completed the programme were more likely to lose ≥5 kg. Outcomes from the phase 1 lifestyle stage influence the selection of the phase 2 intervention. Those who do well in the lifestyle phase are offered FWL and have the highest weight loss by the end of phase 2. Orlistat and LCD are offered for those who failed to lose significant weight with lifestyle alone but do not result in large numbers achieving >5 kg weight loss. Conversely, 83% of the patients who selected FWL lost ≥5 kg. Therefore, the findings of this study suggest a number of important implications to improve future weight management programmes, such as, targeting effective interventions at specific populations and increasing the intensity of phase 2 interventions to improve overall effectiveness. The real-life data showed minimal effect of orlistat and LCD on weight loss, and more research might be needed to confirm their effect. Encouraging women, young people and those from the most deprived areas to complete the programme might improve its overall effectiveness. Further work should be conducted to determine the effective interventions for patients referred to weight management programmes, in order to stratify patients into different treatment modalities, based on results and evidence.

Chapters 3 and 4 evaluated the effectiveness of GCWMS in achieving target weight loss, and a portion of the results showed that patients with diabetes lost less weight than participants without. The SIGN guidelines highlight the drugs treatment plan for individuals with obesity and diabetes. Therefore, in the subsequent chapters (5 and 6), the prescribing pattern for anti-diabetic drugs will be investigated, and the observed effects of these medications on weight change reported.

Chapter 5: Prescribing patterns for weight-neutral, mixed and weight-gaining anti-diabetic medications at Glasgow and Clyde Weight Management Service

5.1 Chapter summary

A number of different anti-diabetic drug groups are used to treat patients with type 2 diabetes. They use different mechanisms to control blood glucose levels and have differential effect on body weight. Previous researchers have studied the prescribing pattern of anti-diabetic medications for patients with diabetes. Some of this has suggested an association between obesity and anti-diabetic medication; accordingly, the SIGN guidelines launched in 2010 highlighted treatment guidance for patients with both diabetes and obesity. The aim of this study was to observe the prescribing pattern for anti-diabetic drugs in subjects with type 2 diabetes and obesity. It was hypothesized that patients with obesity and diabetes were less likely to be prescribed weight-gaining drugs. The second objective of the research was to determine whether the introduction of the SIGN guidelines influenced prescribing practice, in terms of the patterns of weight-neutral, mixed and weight-gaining anti-diabetic drugs prescribed.

A cross-sectional study was carried out including adult individuals of both sexes with type 2 diabetes referred to the GCWMS. Their anti-diabetic drugs were classified into three categories based on their effect on body weight, using the Diabetes Update Guide to Meds & Kit, 2015 and the British National Formulary, 2016 (BNF). These categories included weight-neutral, mixed and weight-gaining anti-diabetic medications. The number and percentage of drug groups prescribed, and the proportion of patients on weight-neutral, mixed and weight-gaining anti-diabetic drugs were reported. Furthermore, a repeat cross-sectional design was used to infer differences in the patterns of the prescribing of anti-diabetic drugs following the introduction of the SIGN guidelines.

A total of 3,063 individuals were included in this study (55.3% females and 44.5% males). The mean BMIs for females and males were 41.1 kg/m^2 and 40.2 kg/m^2, respectively, and overall the mean BMI at baseline for all age groups was lower among patients on weight-gaining anti-diabetic drugs. Metformin was the most commonly prescribed drug for patients with obesity and type 2 diabetes, and sulfonylureas (SUs) and thiazolidinediones (TZDs) were the least prescribed drugs. A total of 47.8% of the subjects were prescribed weight-neutral anti-diabetic drugs and 39.4% were on the mixed drug regimen. A total of 12.7% of the subjects were on drugs known to cause weight gain, and a further respective 11.6% and 13.8% (p =0.13) were on weight-gaining drugs prior to and one year after the SIGN guidelines were issued.

In conclusion, there was no change in the anti-diabetic prescriptions issued by GPs to patients with obesity and type 2 diabetes after the SIGN guidelines were released.

5.2 Introduction

In the UK, the majority of patients with type 2 diabetes are overweight or obese, estimated at 80-90% (Diabetes UK, 2009). The risk of type 2 diabetes in people with obesity (defined as BMI >35 kg/m^2) is between 50-80 times higher than that in those with a BMI <23 kg/m^2 (Chan *et al*., 1994). Obesity is the major risk factor for the development of type 2 diabetes. However, many other factors, such as age, gender and SIMD, may influence the risk of type 2 diabetes. In terms of sex, a study by Sattar (2013) suggested that men's have higher visceral fat levels result in higher liver fat and insulin resistance compared with women of similar BMI. This is consistent with an earlier study by Logue *et al*. (2011) that found that men developed diabetes in a lower BMI range compared with women across the age spectrum. The incidence of type 2 diabetes increases with age, the highest prevalence (10.4% of women and 15.7% of men) being found between 65 and 74 years of age in England (Craig & Mindell, 2008). Furthermore, people with type 2 diabetes are less overweight with increasing age, and older patients may not be treated as aggressively. These factors might affect the prescribing of anti-diabetic drugs - patients with higher BMIs may be prescribed weight-neutral drugs or patients over 70 years of age may be prescribed weight-gaining drugs. Prescription practice may also be influenced by patients' sex. Women are more likely to develop osteoporosis than men with age; the SIGN guidelines (SIGN 116, 2010) recommend that the risk of bone fractures form part of the consideration when treating patients with pioglitazone.

According to evidence, the majority of the oral anti-diabetic medications available are associated with weight gain, which makes the management of type 2 diabetes in individuals with overweight and obesity more challenging (Solini, 2015). According to the SIGN guidelines and the American Association of Clinical Endocrinologists (AACE), patients with obesity and type 2 diabetes should be provided with an individualised intervention, to include a lifestyle intervention, and pharmacotherapy or surgery to promote weight loss, in order to improve glycaemic control.

Treatment for patients with obesity and type 2 diabetes is advised to proceed according to the obesity management algorithm. It is important to follow the algorithm and the guidelines when treating this group of patients, and as general practitioners will be the main prescribers, it is important that they have a clear understanding of why patients with diabetes and obesity require specific treatment plans, unless patients have uncontrolled glycaemic levels (NHS Scotland, 2014).

Due to the availability of numerous classes and the inclusion of multiple drugs in each class, it is essential for physicians to prescribe the most helpful oral hypoglycaemic drug for each patient, depending on their particular situation. Various anti-diabetic drugs can be used to control blood glucose while ensuring weight to remains neutral, such as Biguanides, Glucagon-like peptide-1 agonist (GLP-1 agonists), Dipeptidylpeptidase-4 inhibitors (DPP-IV inhibitors) and Sodium-glucose co-transporter-2 inhibitors (SGLT2 inhibitors). However, some are known to cause weight gain, such as SUs and TZDs (Inzucchi *et al*., 2015). Accordingly, drugs that assist weight to remain neutral or promote weight loss should be the first-line treatment in patients with obesity and type 2 diabetes (Bonora, 2007). However, the decision about which drug treatment to start for patients with diabetes and obesity depends not only on their weight, but also on the drug's efficacy, associated side effects, cost and the patient acceptance of the treatment (Hollander, 2007).

Often, clinical guidelines can take as long as 3 years to be completely implemented (NICE, 2007). While, new guidelines and recommendation regarding drugs treatments are expected to be rapidly transferred into clinical practice, in reality, there is often considerable variation in the compliance of clinicians. Titler (2008) suggested that implementing the change in the guidelines might take several weeks to months, based on the nature of the practice change. A previous study by Cuspidi *et al*., (2002) investigated whether GPs in Italy manage patients with hypertension according to the recommendation of the WHO (1999) guidelines. Six hypertension outpatient centres participated and 228 patients were included in the study. It was found that only 10% of the physicians were complied with the guidelines; the researcher suggested that the impact of guidelines on patients' treatment in clinical practice seemed peripheral. Therefore, it might be possible to test a hypothesis that there would be a reduction in proportion of patients being prescribed weight-gaining anti-diabetic medication after the publication of SIGN guidelines in 2010. However, it might be argued that the introduction of the guidelines need not necessarily have a measurable effect in the situation that prescribing was already being performed completely in accordance with good clinical practice.

Little evidence exists regarding the patterns of the prescription of anti-diabetic medications to patients with diabetes and obesity referred to weight management services. The aim of this research is to describe the proportion of patients with diabetes referred to the GCWMS from 2008 to 2014 on weight-neutral, mixed and weight-gaining anti-diabetic medications, and to compare the results based on three phases:

Phase 1: Before the SIGN guidelines were released in March 2010 (from January 2008 to the end of February 2010).

Phase 2: A one-year-long transitional phase (from March 2010 to February 2011).

Phase 3: After the release of the guidelines (from March 2011 to May 2014).

In addition, the study also aims to evaluate the impact of age, sex and SIMD on anti-diabetic drugs prescribing. Hence, it could conceivably be hypothesised that a reduction would be witnessed in the proportion of patients being prescribed weight-gaining anti-diabetic medication after the publication of the SIGN guidelines in 2010.

5.3 Materials and methods

5.3.1 Study procedure

Once the patients were referred, all medications were imported into the GCWMS database from the Scottish Care Information (SCI) gateway referral. Search terms were used to ascertain the anti-diabetic drugs used for classification and coding according to the BNF, 2016 categories. The anti-diabetic medications were recorded in the GCWMS database using their generic names or their trade names.

These drugs were classified into seven groups: Biguanides, DPP-IV inhibitors, GLP-1 agonists, SGLT2 inhibitors, TZDs, SUs and insulin. Drugs in all of these anti-diabetic drug groups were available in the UK in 2015, and their different trade names in addition to any combined medications available in the UK were identified using the Diabetes Update Guide to Meds & Kit (Diabetes UK, 2015), and BNF 2016 **(Table 5-1)**. Based on the SIGN guidelines and a range of RCTs (Pi-Sunyer, 2008; Astrup *et al*., 2009; Phung *et al*., 2010; Astrup *et al*., 2012) (page 72-75), the drugs were then categorised according to their effect on body weight as weight-neutral, mixed and weight-gaining drugs. With respect to the strength of evidence used in the formulation of these guidelines, high-quality evidence, such as meta-analyses and systematic reviews of RCTs, or RCTs with a very low or low risk of bias, was used to make recommendations for patients with obesity.

After this, each category was classified into different groups, according to whether the expected weight change outcome might increase or decrease when patients used a combination of drug groups from the same category.

1. Weight neutral:

1a. Metformin only

1b. Metformin +DPP-IV +/OR GLP-1 +/OR SGLT2

2. Mixed:

2a. **(SUs)** AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2)

2b. **(TZDs + SUs) OR (TZDs)** AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2)

3. Weight gaining:

3a. SUs only

3b. SUs + TZDs

3c. any combination including insulin

5.3.2 Data source, inclusion and exclusion criteria

Participants of both sexes, aged ≥18 years, referred to the GCWMS between 2008 and 2014 using anti-diabetic medication were included. Any patient on insulin only or on any combination not described above was excluded. Initial numbers in each subgroup, mean BMI, BMI categories, sex, SIMD and age were identified, and the subgroups combined according to their effect on body weight (i.e. 1a +1b and 2a +2b). A comparison was then performed between the number and the types of anti-diabetic drugs given to patients referred before the SIGN guidelines, during the first year, and one year after the guidelines were released.

5.3.3 Statistical methods

The results were reported as number, mean ± SD and percentages. The differences in patient characteristics, such as mean age and BMI, were tested using an independent t- test for the following two groups:

- Patients with type 2 diabetes and obesity referred to the GCWMS on weight-neutral were compared with those referred on mixed drugs.

- Patients with type 2 diabetes and obesity referred to the GCWMS on weight-neutral were compared with those referred using weight-gaining medication.

A Chi-square test was used to measure the categorical variables; in addition, the differences between the proportions of patients referred (before and one year after the SIGN guidelines were published) on weight-gaining drugs were tested using the chi-square test. A limited number of studies suggested there was an association between the prescribing of anti-diabetic drugs and the baseline of age, sex, BMI and SIMD (Kamrai & Sac deva, 2010; Leal *et al*., 2013); therefore, a stratified analysis was used to control the effect of these known determinants (confounding factors) among the variables. *P*-value was considered as significant if <0.05 and all the statistical analyses were carried out using State version 12.1 (StataCorp, College Station, Texas).

SU	TZD	SGLT2 Inhibitors	GLP-1 Agonists	DPP-IV Inhibitors	Biguanides	Insulin	Combined Medications
Glibenclamide **(Daonil®) (Euglucon®)**	Pioglitazone **(Actos®)**	Canagliflozin **(Invokana®)**	Liraglutide **(Victoza®)**	Sitagliptin **(Januvia®)**	Metformin **(Glucophage®)**	Insulin Aspart **(Novorapid®)**	Pioglitazone + Metformin **(Competact®)**
Gliclazide **(Diamicron®) (Diamicron Mr®)**	Rosiglitazone (**Avandia®)**	Dapagliflozin **(Forxiga®)**	Exenatide **(Bydureon®) (Byetta®)**	Vildagliptin **(Galvus®)**	Metformin M/R **(Glucophage Sr®)**	Insulin Lispro **(Humalog®)**	Vildagliptin + Metformin **(Eucreas®)**
Glipizide (**Minodiab®**) **(Glibenese®)**		Empagliflozin **(Jardiance®)**	Lixisenatide **(Lyxumia®)**	Saxagliptin **(Onglyza®)**		**Actrapid®** Humulin S®	Sitagliptin + Metformin **(Janumet®)**
Tolbutamide **(Tolbutamide®)**				Alogliptin **(Vipidia®)**		Insulin Glargine **(Lantus®)**	Saxagliptin + Metformin **(Komboglyze®)**
				Linagliptin **(TRAJENTA®)**		**Novomix® 30**	Alogliptin + Metformin **(Vipdomet®)**
Glimepiride **(Amaryl®)**						**Humulin M3®**	Linagliptin + Metformin **(Jentadueto®)**
						Humalog® Mix25, **Humalog®** Mix50	Rosiglitazone + Metformin **(Avandamet®)**
						Humulin® R	
						Levemir®	

Table 5-1 Medications available in the UK in 2015 (according to The Diabetes Update Guide to Meds & Kit, 2015 and BNF, 2016).

5.4 Results

5.4.1 Baseline characteristics

In total, 3,193 of the subjects referred to the GCWMS from 2008 to 2014 were taking anti-diabetic drugs: 72 individuals were excluded because they were on insulin treatment only, and 58 patients were excluded because they were on different combinations of anti-diabetic drugs to those described above. Of the remainder, 3,063 individuals met the inclusion criteria for this study. Out of the 3,063 participants, 1,693 (55.3%) were females and 1,364 (44.5%) were males.

The participants were further categorised based on their age: 112 (3.6%) individuals belonged to the age group 18-29 years; 280 (9.1%) patients were aged 30-39 years; 676 (22.0%) patients were aged group 40-49 years; 986 (32.1%) were aged 50-59 years; 757 (24.7%) were aged 60-69 years; and 252 (8.2%) were aged ≥70 years. Mean weights for males and females were 122.4 and 105.5 kg, respectively (p =0.001); however, this is because on average the men were also taller. There was a small but significant difference showing that the referred men were less obese than the women. The mean BMIs for males and females was 40.2 and 41.1 kg/m^2, respectively (p =0.0004). It is estimated that 20.4% of the individuals had a BMI in the range 30-34.9, 31.2% were in the range 35-39.9, 38.6% were in the range 40-49.9, and 9.7% were in the range ≥50 kg/m^2; furthermore, 46.8% of the patients with diabetes were from the most deprived quintile and 11.3% from the least deprived quintile.

The weight-neutral drug category of Metformin (group 1a) was the most commonly individually prescribed drug (43.7%), followed by mixed drugs category of SUs with one or more weight-neutral anti-diabetic drug (group 2a) (25.5%). Whereas, the least prescribed drug group included weight gaining drugs category of SUs plus TZDs (group 3b) (1.70%) **(Table 5-2)**.

5.4.2 The association between BMI and anti-diabetic drugs prescribing

It can be seen from Table 5-2 that there was an association between a patient's BMI and their drugs prescription. People with higher BMIs were less likely to be prescribed weight-gaining drugs. However, patients with higher BMIs were more likely to be prescribed metformin (1a) (p =0.015). Meanwhile, a higher proportion of participants with lower BMIs were prescribed weight gaining drugs (group 3a and 3b) compared with those with BMI ≥40 kg/m^2. The strongest association found was between BMI and the prescription of drugs. However, it remains necessary to investigate the possibility that age and sex might be confounding factors.

Anti-diabetic drugs category	**30-34.9**		**35–39.9**		**40–49.9**		**≥50**		**Total**		***P*-value**
1-Weight-neutral	N	%	N	%	N	%	N	%	N	%	
1a	244	**39.1**	412	**43.0**	535	**45.2**	148	**49.3**	1339	**43.7**	**0.015**
1b	21	**3.4**	36	**3.8**	55	**4.6**	14	**4.7**	126	**4.1**	**0.51**
Total	265	**42.5**	448	**46.8**	590	**49.8**	162	**54.0**			
2- Mixed											
2a	182	**29.1**	251	**26.2**	283	**24.0**	62	**20.6**	778	**25.4**	**0.019**
2b	76	**12.2**	118	**12.3**	182	**15.4**	53	**17.7**	429	**14.0**	**0.028**
Total	258	**41.3**	369	**38.5**	465	**39.4**	115	**38.3**			
3-Weight-gaining											
3a	35	**5.6**	61	**6.4**	41	**3.5**	8	**2.7**	145	**4.7**	**0.003**
3b	19	**3.0**	18	**1.9**	9	**0.7**	4	**1.3**	50	**1.7**	**0.003**
3c	47	**7.5**	60	**6.3**	78	**6.6**	11	**3.7**	196	**6.4**	**0.15**
Total	101	**16.1**	139	**14.6**	128	**10.8**	23	**7.7**			
Number of patients	624 (20.4%)		956 (31.2%)		1,183 (38.6%)		300 (9.7%)		3,063		

Table 5-2 Number and percentage of anti-diabetic group based on the patients' BMI. N: Number. *P*-values were determined using the Chi-square test for trend (p-value <0.05 considered statistically significant). (1a. Metformin only; 1b. Metformin+DPP-IV+/OR GLP-1 +/OR SGLT2; 2a. (SUs) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2); 2b. (TZDs + SUs) OR (TZDs) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2); 3a. SUs only; 3b. SUs + TZDs; 3c. Any combination including insulin).

5.4.3 The association between age and anti-diabetic drugs prescribing

Table 5-3 shows an association between age and drug prescriptions; older people (≥40 years) were more likely to be prescribed mixed-drugs (2a, 2b) (p =0.001) or weight-gaining drugs (SUs (3a) and SUs plus TZDs (3b)) (p =0.001 and 0.046, respectively). However, younger participants (18-29 years) were more likely to be prescribed metformin (1a) (p =0.001), than older people (≥60 years). This association might be due to the effect of BMI, which will be explored later. For example, as older patients generally have lower BMIs than younger ones, it is possible that the effect might be a result of differences in BMI.

Anti-diabetic category	18-29		30–39		40–49		50–59		60–69		≥70		Total		*P*-value
1-Weight-neutral	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
1a	95	**84.8**	174	**62**	310	**45.9**	411	**41.7**	256	**33.8**	93	**36.9**	1339	**43.7**	**0.001**
1b	1	**1**	15	**5.4**	38	**5.6**	42	**4.2**	25	**3.3**	5	**2**	126	**4.1**	**0.033**
Total	96	**85.8**	189	**67.4**	348	**51.5**	453	**45.9**	281	**37.1**	98	**38.9**			
2- Mixed															
2a	7	**6.2**	52	**18.5**	162	**24**	270	**27.4**	225	**29.7**	62	**24.6**	778	**25.4**	**0.001**
2b	3	**2.5**	15	**5.4**	93	**13.8**	150	**15.2**	128	**17.0**	40	**15.9**	429	**14.0**	**0.001**
Total	10	**8.7**	67	**23.9**	255	**37.8**	420	**42.6**	353	**46.7**	102	**40.5**			
3-Weight-gaining															
3a	1	**1**	4	**1.5**	25	**3.7**	42	**4.2**	46	**6.0**	27	**10.7**	145	**4.8**	**0.001**
3b	0	**0**	1	**0.3**	8	**1.2**	17	**1.7**	15	**2.0**	9	**3.6**	50	**1.7**	**0.046**
3c	5	**4.5**	19	**6.8**	40	**5.9**	54	**5.5**	62	**8.2**	16	**6.3**	196	**6.4**	**0.26**
Total	6	**5.5**	24	**8.6**	73	**10.8**	113	**11.4**	123	**16.2**	52	**20.6**			
Number of patients	112 (3.6%)		280 (9.1%)		676 (22.0%)		986 (32.2%)		757 (24.7%)		252 (8.2%)		3,063		

Table 5-3 Number and percentage distribution of anti-diabetic drugs category based on age group of patients. N: Number. *P*-values were determined using the Chi-square test for trend (*p*-value <0.05 considered statistically significant). (1a. Metformin only; 1b. Metformin+DPP-IV+/OR GLP-1 +/OR SGLT2; 2a. (SUs) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2); 2b. (TZDs + SUs) OR (TZDs) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2); 3a. SUs only; 3b. SUs + TZDs; 3c. any combination including insulin).

5.4.4 The association between sex and anti-diabetic drugs prescribing

Table 5-4 shows that there was an association between sex and anti-diabetic drugs prescriptions; generally, men were more likely to be prescribed weight-gaining drugs (14.3%) than women (11.5%) (p =0.02). Moreover, men were more likely to be prescribed mixed-drugs (group 2a and 2b) than women. On the other hand, metformin (group 1a) alone was prescribed more frequently to females than males. The data showed it was prescribed to 49.7% of females and 36.0% of the males (p =0.001). The factor responsible for this difference might not necessarily be the sex of the patients. It may depend on the weight of the patients, which will be explored later.

Anti-diabetic drug(s) category	**Males**		**Females**		**Total**		***P*-value**
	N	%	N	%	N	%	
1-Weight-neutral							
1a	492	**36.0**	842	**49.7**	1334	**43.7**	**0.001**
1b	76	**5.5**	50	**3.0**	126	**4.1**	**0.001**
Total	568	**41.6**	892	**52.7**			
2- Mixed							
2a	384	**28.1**	394	**23.3**	778	**25.5**	**0.002**
2b	217	**16.0**	212	**12.5**	429	**14.0**	**0.007**
Total	601	**44.1**	606	**35.8**			
3-Weight-gaining							
3a	87	**6.4**	57	**3.4**	144	**4.7**	**0.001**
3b	22	**1.6**	28	**1.6**	50	**1.6**	**0.92**
3c	86	**6.3**	110	**6.5**	196	**6.4**	**0.82**
Total	195	**14.3**	195	**11.5**			**0.02**
Number of patients	1,364 (44.5%)		1,693 (55.3%)		3,057 (6 missing)		

Table 5-4 Number and percentage of anti-diabetic groups based on the patients' sexes. N: Number. *P*-values were determined using the Chi-square test for trend (p-value <0.05 considered statistically significant). (1a. Metformin only; 1b. Metformin+DPP-IV+/OR GLP-1 +/OR SGLT2; 2a. (SUs) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2); 2b. (TZDs + SUs) OR (TZDs) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2); 3a. SUs only; 3b. SUs + TZDs; 3c. Any combination including insulin).

5.4.5 The association between SIMD and anti-diabetic drugs prescribing

The socioeconomic status of the patients did not correlate with the prescribing patterns for anti-diabetic drugs; the *p*-value for each group of drugs was >0.05 as seen in **(Table 5-5)**.

Anti-diabetic drugs category	Most deprived		2		3		4		Least deprived		Total		*P*-value
1-Weight-neutral	N	%	N	%	N	%	N	%	N	%	N	%	
1a	628	**43.7**	255	**45.4**	176	**44.1**	120	**39.3**	154	**44.3**	1333	**43.7**	**0.54**
1b	62	**4.3**	24	**4.3**	17	**4.3**	10	**3.3**	13	**3.7**	126	**4.1**	**0.92**
Total	690	**48**	279	**49.7**	193	**48.4**	130	**42.6**	167	**48.0**			
2- Mixed													
2a	367	**25.5**	144	**25.6**	99	**24.8**	81	**26.5**	82	**23.6**	773	**25.4**	**0.91**
2b	201	**14.0**	72	**12.8**	56	**14.0**	45	**14.7**	55	**15.8**	429	**14.0**	**0.78**
Total	568	**39.5**	216	**38.4**	155	**38.8**	126	**41.2**	137	**39.4**			
3-Weight-gaining													
3a	62	**4.3**	21	**3.7**	20	**5.0**	22	**7.2**	19	**5.5**	144	**4.8**	**0.16**
3b	20	**1.4**	9	**1.6**	7	**1.8**	6	**2.0**	8	**2.3**	50	**1.7**	**0.78**
3c	96	**6.7**	37	**6.6**	24	**6.0**	21	**6.91**	17	**4.9**	195	**6.4**	**0.77**
Total	178	**12.4**	67	**11.9**	51	**12.8**	49	**16.1**	44	**12.6**			
Number of patients	1,436 (46.8%)		562 (18.3%)		399 (13.0%)		305 (10.0%)		348 (11.3%)		3,050 (11 missing)		

Table 5-5 Number and percentage of anti-diabetic group based on the patients' socioeconomic status. *P*-values were determined using the Chi-square test for trend (*p*-value <0.05 considered statistically significant). (1a. Metformin only; 1b. Metformin+DPP-IV+/OR GLP-1 +/OR SGLT2; 2a. (SUs) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2); 2b. (TZDs + SUs) OR (TZDs) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2); 3a. SUs only; 3b. SUs + TZDs; 3c. Any combination including insulin).

As the main association was between BMI and drug prescribing, the other factors are viewed as confounders of this association. In order to further investigate the relationship between sex and the prescription of anti-diabetic drugs, the results were subdivided into more specific BMI ranges **(Table 5-6)**.

Drugs	**BMI categories (kg/m^2)**							
	30-34.9		**35-39.9**		**40-49.9**		**≥50**	
	Sex							
	F N (%)	**M** N (%)	**F** N (%)	**M** N (%)	**F** N (%)	**M** N (%)	**F** N (%)	**M** N (%)
Weight-neutral	158 (47.6)	105 (36.2)	274 (51.6)	172 (40.7)	371 (54.6)	218 (43.5)	115 (57.5)	47 (47.0)
Mixed	120 (36.1)	138 (47.6)	181 (34.1)	188 (44.4)	235 (34.5)	230 (45.9)	70 (35.0)	45 (45.0)
Weight-gaining	54 (16.3)	47 (16.2)	76 (14.3)	63 (14.9)	74 (10.9)	53 (10.6)	15 (7.5)	8 (8.0)
Total	332 (100)	290 (100)	531 (100)	423 (100)	680 (100)	501 (100)	200 (100)	100 (100)
***P*-value for weight-gaining drugs**	0.98		0.80		0.86		0.88	

Table 5-6 Stratification of the relationship between sex and the prescribing of anti-diabetic drugs by BMI (N: Number; F: Female; M: Male).

Table 5-4 shows that women were more likely to be prescribed weight-neutral drugs and men more likely to be prescribed weight-gaining drugs (group 3a). Following stratification by BMI category, Table 5-6 illustrated that there was no difference in the proportion of men and women on weight-gaining drugs when take into account BMI (*P*-values for the different BMI categories were 0.98, 0.80, 0.86 and 0.88). For example, for patients with a BMI between 30 and 34.9 kg/m^2, the percentages of women and men on weight-gaining drugs were 16.3% and 16.2% respectively. Therefore, this association was not because of the patients' sex itself, but might have been because men in the weight-gaining group (group 3a) were lighter than women; the mean BMIs of men and women were 38.5 kg/m^2 and 39.2 kg/m^2 respectively.

With regard to the association between age and drug prescribing, Table 5-3 shows that older people were more likely to be prescribed weight-gaining anti-diabetic drugs, while younger people were more likely to be prescribed weight-neutral anti-diabetic drugs. However, this relationship may be explained by the patient's BMI, as older patients were more likely to be lighter. In order to further investigate the relationship between age and the prescription of anti-diabetic drugs, the results were subdivided into finer BMI ranges **(Table 5-7)**.

Drugs	**BMI categories (kg/m^2)**																							
	30-34.9						**35-39.9**						**40-49.9**						**≥50**					
	Age categories (year)																							
	18-29 N %	**30-39** N %	**40-49** N %	**50-59** N %	**60-69** N %	**≥70** N %	**18-29** N %	**30-39** N %	**40-49** N %	**50-59** N %	**60-69** N %	**≥70** N %	**18-29** N %	**30-39** N %	**40-49** N %	**50-59** N %	**60-69** N %	**≥70** N %	**18-29** N %	**30-39** N %	**40-49** N %	**50-59** N %	**60-69** N %	**≥70** N %
Weight-neutral	9 75	30 73.1	46 45.5	80 42.1	69 35	31 37	25 89.3	54 71.1	107 52.9	128 42.4	97 38.8	37 37.8	52 86.7	80 63	141 51.3	197 50.3	96 35.7	24 40	10 83.3	25 69.4	54 55.1	48 47	19 6.4	6 54.5
Mixed	1 8.3	7 17.1	41 40.56	81 42.6	92 46.7	36 43.4	1 3.5	15 19.7	71 35.1	140 46.4	108 43.2	34 34.7	6 10	37 29.1	106 38.5	154 39.3	135 50.2	27 45	2 16.7	8 22.2	37 37.7	45 44.1	18 34.9	5 45.4
Weight-gaining	2 16.7	4 9.7	14 13.8	29 15.2	36 18.3	16 19.3	2 7.1	7 9.2	14 11.9	34 11.3	45 18	27 27.5	2 3.3	10 7.9	28 10.1	41 10.5	38 14.1	9 15	0 0	3 8.3	7 7.1	9 8.8	4 9.7	0 0
Total	12 100	41 100	101 100	190 100	197 100	83 100	28 100	76 100	202 100	302 100	250 100	98 100	60 100	127 100	275 100	392 100	269 100	60 100	12 100	36 100	98 100	102 100	41 100	11 100
***P*-value**	0.002						0.001						0.001						0.26					

Table 5-7 Stratification of the relationship between age and the prescribing of anti-diabetic drugs by BMI (N: Number; %: percentage).

As the weight-gaining drugs were more likely to be prescribed to those with a lower BMI (Table 5-2), following the subdivision of patients according to age, it was found that the association between BMI and drug prescribing was confounded by the patient's age. Table 5-7 shows that quite a similar proportion of patients aged between 30 and 39 years (9.7%, 9.2%, 7.9% and 8.3%) were using weight-gaining drugs in the four different BMI categories (30-34.9, 35-39.9, 40-49.9 and $\geq$50 kg/m^2 respectively). Among those patients with a BMI of at least 50 kg/m^2, the proportion using weight-gaining drugs was generally age-independent.

Alternatively, Table 5-3 showed that a higher proportion of older people used weight-gaining anti-diabetic drugs compared with younger patients. Furthermore, Table 5-7 shows that among the patients with a BMI of between 30 and 34.9 kg/m^2, a higher proportion (18.3%) of patients aged between 60 and 69 years used weight-gaining drugs compared to the proportion (9.7%) of patients aged 30-39 years. This may indicate that people lose more weight at older ages, which may result in them being prescribed more weight-gaining anti-diabetic drugs. Therefore, it can be concluded that the initial BMI may partially confound the relationship between patient age and drug prescribing.

5.4.6 Characteristics and proportion of patients in different anti-diabetic categories

Table 5-8 shows patients prescribed weight-neutral drugs had mean BMIs 2 kg/m^2 higher than those prescribed weight-gaining drugs, and this difference was statistically significant (p =0.001). In addition, individuals who were prescribed weight-neutral drugs were younger than those on mixed or weight-gaining drugs (mean ages were 50.7, 55.6 and 56.6 years, respectively; and this difference was statistically significant (p =0.001). Meanwhile, there was no difference in the initial BMIs between those on weight-neutral drugs and patients on mixed drugs (p =0.08).

Drug categories	**subgroup**	**Total (*n*)**	**Mean BMI** ± SD	***p-value***	**Mean weight** ± SD	**Mean age** ± SD	***p-value***
1.Weight-neutral	1a (*n* =1,339) 1b (*n* =126)	1,465	41.2 (±7.0)	**1&2 *p*-value= 0.08**	113.0 (±22.8)	50.7 (±12.9)	**1&2 *p*-value= 0.001**
2. Mixed	2a (*n* =778) 2b (*n* =492)	1,207	40.7 (±7.0)	**1&3 *p*-value= 0.001**	113.8 (±22.7)	55.6 (±10.2)	**1&3 *p*-value= 0.001**
3. Weight gaining	3a (*n* =145) 3b (*n* =50) 3c (*n* =196)	391	39.2 (±6.2)		108.5 (±21.6)	56.6 (±11.5)	

Table 5-8 Characteristics of included patients depending on type of anti-diabetic categories. *P*-values were determined using a t-test (*p*-value <0.05 considered statistically significant) (SD: standard deviation; *n*: number).

5.4.7 Proportion of patients in different anti-diabetic categories after the SIGN guidelines were released

Overall, respectively, 47.8%, 39.4% and 12.7% of the included patients were on weight-neutral, mixed and weight-gaining anti-diabetic medication. The proportion of patients taking weight-neutral drugs before March 2010 was 48.2%, compared with 46.8% during the first year and 48.5% a year after the guidelines established. Likewise, a higher proportion of patients were prescribed weight-gaining anti-diabetic drugs (13.8%) a year after the publication of the current SIGN guidelines, compared with before the guidelines were released (11.6%), although this difference was not statistically significant (p =0.13) **(Table 5-9)** and **(Figure 5-1)**.

Category	N of all patients (total) (*n* =3,063)	%	Before the guidelines (*n* =1,037) (from January 2008 to February 2010)	%	Transitional phase (for a year) (*n* =1,038) (from March 2010 to February 2011)	%	After publication of guidelines (*n* =988) (from March 2011 to May 2014)	%
1.Weight-neutral	1,465	47.8	500	48.2	486	46.8	479	48.5
2. Mixed	1,207	39.4	416	40.1	418	40.3	373	37.7
3. Weight-gaining	391	12.7	121	**11.6**	134	**12.9**	136	**13.8**
p-value = **0.13** (The difference in the proportion of patients on weight-gaining drugs before and after the SIGN guidelines were published was examined).								

Table 5-9 Proportion of patients referred in different anti-diabetic drugs categories based on three phases of the SIGN guidelines. *P*-values were determined using the Chi-square test (*p*-value <0.05 considered statistically significant).

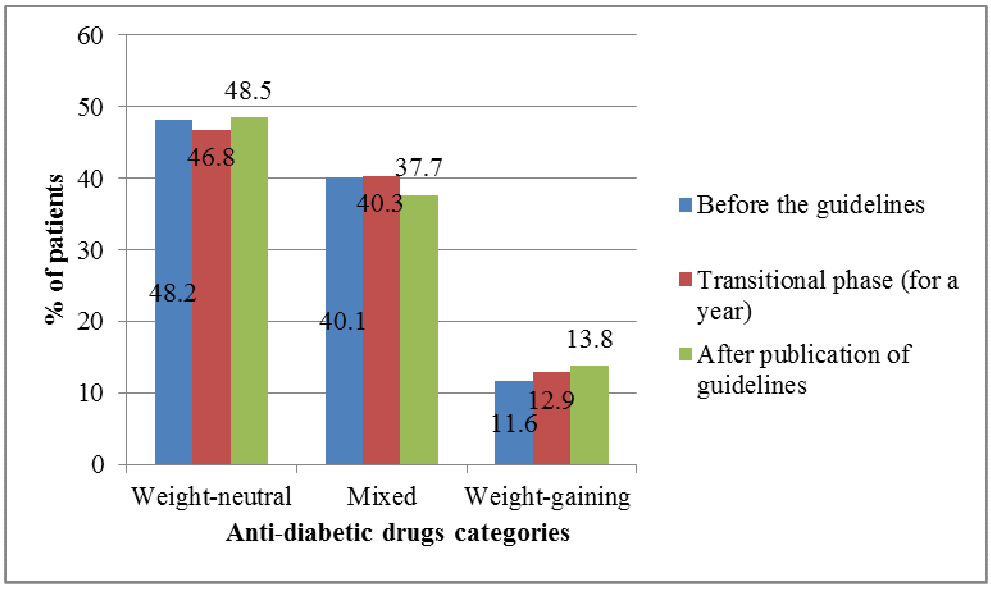

Figure 5-1 Proportion of patients by GP prescribing pattern of anti-diabetic drugs before, during one year, and one year after the release of the SIGN guidelines.

5.4.8 Prescribing trends over the time

In order to explore whether there were any year-on-year trends towards gradually improving compliance with guidelines, the prescribing trend for the three categories of anti-diabetic medications were reported. **Figure 5-2** shows no clear trend over time for patients prescribed weight-neutral drugs. The increase in the prescribing percentage of weight-neutral drugs seen in the final year (2014) might be a result of changes in the groups of drugs approved for the treatment of type 2 diabetes since 2013. However, the only convincing trend over time was a small increase in the volume of weight-gaining drugs prescribed, although it is not clear if any change occurred after the release of the SIGN guidelines in 2010. As a result, there is no indication of a change in practice.

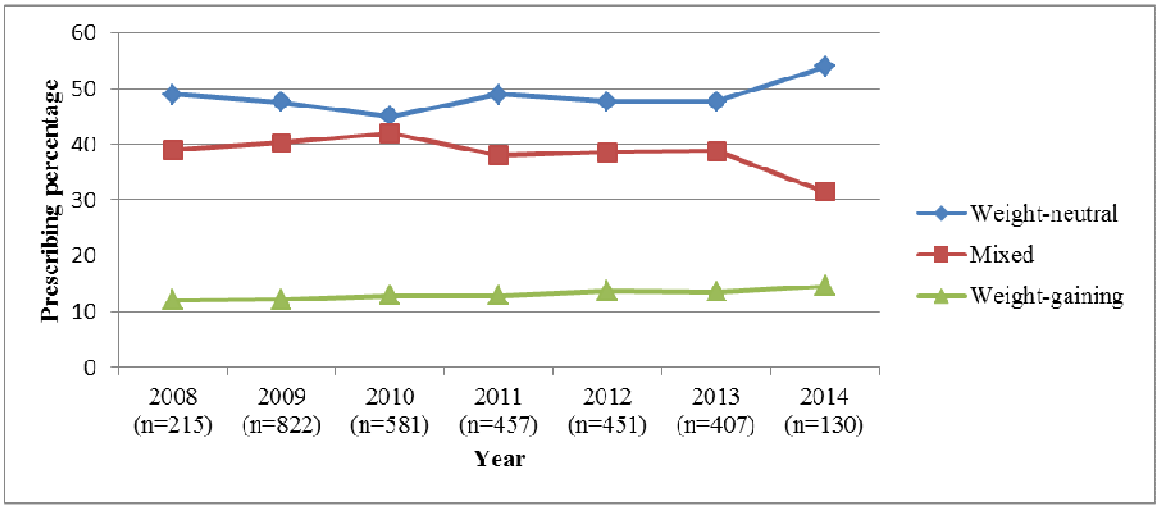

Figure 5-2 Yearly prescribing trend for different anti-diabetic drugs categories from 2008 to 2014 for patients who referred to the GCWMS.

Therefore, a number of other factors (for example, the lower BMIs of the subjects towards the end of the study) may be responsible for the modest increases in the prescription of weight-gaining drugs. Paradoxically, it was found that people had higher BMIs in later years compared with the earlier years. For instance, the mean BMI of the patients in 2008 was 38.7 kg/m^2, compared to 39.2 kg/m^2 in 2014.

5.5 Summary of the main findings

- The majority of the patients with diabetes were female, aged 40-<70, with BMIs 30-<50, and from the most deprived quintile.
- Metformin was the highest prescribed anti-diabetic drug, and the group of SUs plus TZDs was least prescribed to participants of both sexes. In addition, metformin was prescribed more to women than men; and a higher proportion of men were prescribed SUs groups compared with women.
- The rate of metformin prescription rose as age decreased and BMI increased. However, the frequency with SU and SUs + TZDs were prescribed was predominantly higher in older patients.
- There was no association between SIMD and anti-diabetic drugs prescribing.
- Patients on weight-neutral anti-diabetic drugs were heavier and younger than those on weight-gaining anti-diabetic drugs.
- Overall, 47.8% of patients referred to the GCWMS and included in this research were on neutral anti-diabetic drugs, and 12.7% were on weight-gaining anti-diabetic drugs.
- There was no significant difference in the prescribing habits noted after the guidelines were established (p =0.13).

5.6 Discussion

The principal objective of this research was to determine whether the prescription of anti-diabetic drugs to patients with type 2 diabetes was consistent with the patients' BMIs. The secondary aim was to investigate whether the introduction in March 2010 of the SIGN guidelines was associated with a change in practices of prescribing anti-diabetic drugs. Additionally, based on the GCWMS data for patients with obesity and type 2 diabetes, the pattern of prescribing anti-diabetic drugs was investigated; as were the effects of age, sex and SIMD. According to the Scottish Diabetes Survey in 2015; at that time, around 5.3% of adults in Scotland had been diagnosed with diabetes and prevalence was higher among men than women (6.0% and 4.5%, respectively) (NHS Scotland, 2015). To our knowledge, this is the first study investigating the proportion of patients with obesity in different anti-diabetic drug categories; whereas previous evaluations of prescribing patterns for anti-diabetic medication in patients with diabetes were carried out at tertiary hospital level irrespective of BMI.

5.6.1 Baseline characteristics

In Scotland, 55.7% of patients diagnosed with type 2 diabetes are male (NHS Scotland, 2014). However, in this research, just 44.6% of the patients with diabetes included in this study were male, as more females had chosen to enrol in the programme. The majority of patients with obesity and diabetes were in the age group 50-59 years, followed by the age group 60-69 years, concurring with previous studies (Shareef *et al*., 2015; Vengurlekar *et al*., 2008). The increasing prevalence of diabetes in these age groups may be consequence of their change in life style, stress, and lack of exercise (Vengurlekar *et al*., 2008). However, the sample might have been biased, as 26.5% of the total patients (n =7,329) who enrolled in the weight management programme were in the 50-59 year age group, which may explain the higher prevalence of diabetes in this group of patients.

5.6.2 Prescribing pattern

As all patients on insulin only were excluded, those that remained were the type 2 diabetes patients. Metformin (group 1a) was the most commonly prescribed drug, which is consistent findings in other research (Shareef *et al*., 2015; Dhanaraj *et al*., 2013, Filion *et al*., 2009; Kamrai & Sachdeva, 2010). The reason for this could be that patients with obesity who have received metformin reportedly gain less weight and present with lower

hypoglycaemic effect than patients on other hypoglycaemic drugs, such as SUs group or TZDs group (Leal *et al*., 2013). A previous study (2-years follow-up) of 3,807 participants, suggested that irrespective of BMI, metformin was the most commonly prescribed drug for patients with diabetes (Hartmann *et al*., 2015). However, this research found that a low proportion of patients were in either the SUs (4.8%) or SUs + TZDs (1.7%) group, possibly because these groups are more prone to causing excessive weight gain meaning they are not ideal for use in patients with obesity. These findings were consistent with a previous study that reported SUs and TZDs were not prescribed for subjects with a BMI between 35-40 kg/m^2 (Kamrai & Sachdeva, 2010).

When reviewing the literature, minimal data were found on the association between patient's age, sex and initial BMIs and anti-diabetic drugs prescribing. Previous studies have also reported that some drugs have an adverse effect on elderly people, such as SUs that may cause hypoglycaemia, and other studies recommend metformin for people with high BMIs. Therefore, these factors might or might not justify prescribing.

5.6.3 Impact of BMI

Metformin was prescribed for individuals with a higher BMI, and weight-gaining drug groups (group 3a and 3b) were prescribed more for patients with a lower BMI. This might be because metformin does not cause weight gain, while SUs and TZDs drug types are avoided in patients with obesity, as they cause excess weight gain (Leal *et al*., 2013; Kamrai & Sachdeva, 2010). This indicates that there was an association between initial BMI and the prescribing of anti-diabetic drugs, although it is possible that these results were confounded by age. The proportion of patients with a relatively low BMI (between 30 and 34.9 kg/m^2) that were prescribed weight-gaining drugs was higher in older patients (that is, those aged at least 70 years) than those aged between 18 and 29 years. Therefore, the results may show an inverse relationship between BMI and age when prescribing anti-diabetic drugs.

There was an association between sex and developing diabetes; this may be explained by a previous study that investigated the relationship between sex and BMI at diabetes diagnosis in Scotland. The large (n =95,059) study concluded that men were diagnosed with type 2 diabetes at lower BMIs than women (Logue *et al*., 2011). The potential mechanisms for this include men having more visceral and hepatic fat than women and being less insulin-sensitive (Geer and Shen, 2009). However, the current results

concluded that sex did not influence the relationship between BMI and anti-diabetic drugs prescribing. The DiaRegis cohort study (*n* =3,807) reported an increased likelihood of treatment with metformin and GLP-1 drugs among subjects with a BMI of ≥30 kg/m^2, and a lower probability of treatment with SUs or insulin (Hartmann *et al*., 2015).

5.6.4 Impact of age

The current research shows an association between age and anti-diabetic drugs prescribing. For example, there was a statistically significant difference in metformin prescribing in different age groups, particularly between young and the old participants (chi-square test represent *p*-value =0.001). This shows that metformin was prescribed more frequently for young patients as monotherapy, while older patients required a combination of anti-diabetic drugs to achieve better glycaemic results. On the other hand, a previous study of 492 patients from Indian hospital, found metformin was prescribed more for older people and the authors suggested this might be due to the increase risk of hypoglycaemia in elderly people who are also being treated with SUs; consequently, metformin is a good option for controlling hypoglycaemia (Kamrai & Sachdeva, 2010). These differences might also explain the effect of other confounding factors, such as initial BMI. This research suggested that the relationship between patients' ages and the prescribing of anti-diabetic drugs was confounded by the initial BMIs for those with BMI ≥50 kg/m^2. Young patients have higher BMIs, which would explain the higher prescribing of weight-neutral anti-diabetic drugs in this group. An equivalent relationship was seen in older patients, whose lower BMIs might explain the increase in the prescription of weight-gaining anti-diabetic drugs. Earlier findings confirmed that there was a marked decrease in patients' BMIs in line with the increased in age at the time of diabetes diagnosis (Logue *et al*., 2011).

5.6.5 Impact of sex

Other observations include that metformin was prescribed more in females than in males, while SUs were prescribed more in males. These findings are consistent with previous results carried reported in the Netherlands, in a study that investigated the new revised guidelines for the treatment with hypoglycaemic agents between 1998 and 2003 (Lub *et al*., 2006). This might also be due to the fact that a number of females stopped taking SUs to avoid weight gain, particularly as a result of oedema, switching to metformin to aid glycaemic control and promote weight loss or remain neutral (Lub *et al*., 2006). The

current research suggested an association between sex type and anti-diabetic drugs prescribing, but there were other confounding factors that might explain this relationship, such as BMI. Obviously, women were heavier than men at the baseline, which may explain the higher rate of prescribing of weight-neutral anti-diabetic drugs. In conclusion, the current results were consistent with a previous study by Ewenighi *et al*. (2012), which found that only age and initial BMI could influence the prescribing of anti-diabetic drugs.

5.6.6 Prescribing before and after release of the SIGN guidelines

This research found no significant difference between the percentages of patients on weight-neutral, mixed and weight-gaining anti-diabetic medications, before and one year after the SIGN guidelines were released. The SIGN guidelines set out a clear treatment plan for patients with diabetes and obesity; aiming to encourage GPs to prescribe the appropriate anti-diabetic drugs for individuals with obesity to elevate the proportion of patients on weight-neutral drugs (SIGN 116, 2010). There was no improvement in the prescribing trend in weight-gaining drugs over the years from 2008 to 2014, which contradicts the current hypothesis. Therefore, the application of trend and regression tests was not considered to be appropriate. The slight increase in weight-gaining drugs prescribing over the years was not contrary to what might have been expected, as weight-gaining prescriptions went up while BMIs also went up. Therefore, this might be explained by GPs' habits or patients' inability to control their blood glucose level. The percentage of patients on weight-gaining anti-diabetic drugs was slightly higher amongst those referred after one year after the SIGN guidelines were released (13.8%), compared with 11.6% before the release of the SIGN guidelines, despite recommendations for GPs to review patient history and the anti-diabetic prescribing patterns for patients before referring them to the GCWMS. Additionally, the recommendation is to try prescribing weight-neutral or mixed drugs for this group of patients; unless there are specific clinical indicators to the contrary.

5.7 Research strengths and limitations

The main strength of this research is the large sample size, derived from one of the largest weight management services available, and providing objective measures of weight and height. To the best of our knowledge, this is the first study comparing the proportion of patients on anti-diabetic drugs before and after the SIGN guidelines were released. In addition, it is the first study to explore the prescribing patterns of anti-diabetic drugs for individuals with obesity and diabetes (the included participants had a BMI of $\geq$30 kg/m^2). Conversely, much of the research to date has concentrated on prescribing patterns for patients with diabetes only (Kamrai & Sachdeva, 2010), describing trends for anti-diabetic prescribing over time (Filion *et al*., 2009). Selection bias was minimal, with only 1.8% of patients excluded (on account of their being on drug regimens that could not be classified into one of the groups). The prescribing information is likely to be accurate, as all the medication came through the SCI gateway.

Conversely, one of the weaknesses of this study is potential information bias, as the drugs were categorised according to their effect on body weight alone, instead of looking at each group of drugs on an individual basis. Likewise, the results of the proportion of patients who were on weight-gaining drugs might have been affected by (group 3c), as some of the patients were prescribed insulin where they had uncontrolled glycaemia by oral hypoglycaemic agents. In addition, this study did not show the prescribing patterns for some drugs regimens as classified into three drugs categories. On the other hand, the classification of anti-diabetic drugs in this research was dependent on the SIGN guidelines and a good range of RCTs, which determined the effect of these drugs on body weight. Nevertheless, the SIGN guidelines were released in 2010, and a group of anti-diabetic drugs (SGLT2 inhibitors) were subsequently approved for use in 2013. However, this group of drug was issued with new guidelines. This might therefore lead to the conclusion that there was strong evidence of a causal relationship in this classification.

5.8 Research implications

This research confirms that half of individuals with type 2 diabetes referred to the GCWMS took weight neutral-anti-diabetic drugs, and around 12.7% were on weight-gaining anti-diabetes medication. Metformin was the drug most prescribed for patients who are obese with type 2 diabetes, while SUs (group 3a) or SUs plus TZDs (group 3b) were the least prescribed drugs. The results of the research indicate that the prescribing practice for type 2 diabetes was broadly consistent with that recommended in the guidelines and that no significant improvements could be made. In contrast, after the SIGN guidelines were released, there was no change in the proportion of patients on weight-gaining anti-diabetic drugs. Whilst there might be good reasons why they were on them, such as uncontrolled blood glucose, it raises the question about whether it could be lower. Therefore, the SIGN guidelines for treating patients with obesity and type 2 diabetes should be followed by GPs to ensure the prescription of weight-neutral or mixed anti-diabetic drugs for patients who are obese with type 2 diabetes. Due to the limitations in the evidence for the effects of anti-diabetic drugs in enhancing or inhibiting weight gain among participants who had joined the weight management programme, the effect of these drugs will be observed in the next chapter. Further implications will be discussed in chapter 7.

Chapter 6: The association between anti-diabetic drug prescribing and weight change

6.1 Chapter summary

Many of the anti-diabetic agents used to target hyperglycaemia are associated with weight gain, which as explained in the previous chapter, creates an additional challenge when treating patients with obesity and type 2 diabetes. However, some anti-diabetic drug groups are known to cause weight neutral or in some cases cause weight loss. The objective of this research was to study the effect of baseline anti-diabetic drugs on weight change for participants enrolled in a lifestyle change programme at the GCWMS.

An intervention cohort study was conducted using baseline anti-diabetic drugs data pertaining to a group of participants aged ≥18 years, of both sexes, with type 2 diabetes who had attended at least 2 sessions in the lifestyle phase of the GCWMS. Based on the BNF and Diabetes Update Guide to Meds & Kit, 2015, the anti-diabetic drugs prescribed were classified into three categories: weight-neutral, mixed and weight-gaining. Mean and percentage weight loss from the different anti-diabetic group and the different categories were reported and analysed using a t-test. In addition, the mean weight change of the total number of patients who attended the lifestyle phase, 5 kg and 5% weight loss were reported.

Of the 998 eligible participants, 459 (46%), 412 (41.3%) and 127 (12.7%) individuals were on weight-neutral, mixed and weight-gaining anti-diabetic drugs, respectively. Patients taking the weight-gaining drugs had poorer outcomes compared with those on weight-neutral drugs. Mean weight changes for all patients on weight-gaining and weight-neutral anti-diabetic drugs was -2.5 kg (95% CI: -3.2 to -1.8 kg) and -3.3 kg (95% CI: -3.8 to -2.9 kg) (p =0.05), respectively. In terms of completion, patients on weight-neutral drugs lost more weight than those on weight-gaining drugs; with mean weight changes of -4.9 kg (95% CI: -5.5 to -4.2 kg) and -3.3 kg (95% CI: -4.2 to -2.5 kg), respectively (p =0.005). In contrast, there was no significant difference between the two groups, in terms of mean percentage weight.

In conclusion, patients on weight-neutral anti-diabetic drugs had a greater outcome compared with those on weight-gaining drugs. There may be good reasons to prescribe weight-gaining medications, however, weight gain could worsen blood glucose. It may be possible to improve weight loss by prescribing mixed or weight-neutral drugs instead.

6.2 Introduction

In the past 20 years, new anti-diabetic drugs have been released and additional drugs have been developed to control blood glucose (Hollander, 2007). The mechanisms of these drugs might alter body weight by enhancing weight loss or promoting additional weight gain (Krentz, 2008). The majority of people diagnosed with type 2 diabetes are overweight or obese, and new groups of anti-diabetic drugs have recently been established for use in the management of type 2 diabetes associated with obesity (Krentz, 2008). Although, it is a challenge to treat individuals with type 2 diabetes and obesity, due to some of the anti-diabetic agents, such as TZDs and SUs, being associated with weight gain (Kenkre *et al*., 2013), requesting an effective anti-diabetic drug capable of reducing body weight is the best approach to the successful treatment of individuals with type 2 diabetes and obesity (Solini, 2015; Pi-Sunyer, 2009).

The majority of the literature reports that the currently used anti-diabetic drugs that may cause weight to remain neutral or cause weight loss are metformin, GLP-1, DPP-IV and SGLT2; while insulin, SUs and TZDs may cause weight gain. UKPDS suggested that SUs can cause 5 kg weight gain over a 10-year period of treatment (UKPDS, 1998); and another study reported that a 1-4 kg weight gain is associated with using SUs, before body weight steadies after six months (Krentz and Bailey, 2005). In addition, in the PROACTIVE trial, TZDs such as pioglitazone produced an average 3.6 kg weight gain over three years; whereas (Dormandy *et al*., 2005), according to the findings of the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial, rosiglitazone yielded a 2.2 kg weight gain over a four-year period (Gerstein *et al*., 2006). Likewise, in a 16-week study (with a small number of participants: n =14) that evaluated the effect of pioglitazone on glucose uptake, individuals apparently gained weight [3.0 ± 3.0 kg (p <0.001)] (Malone, 2005).

The American Diabetes Association (ADA), and the European Society for the Study of Diabetes (EASD), have recommended that metformin should be used as a first-line treatment for patients with normal weight or those who are obese with type 2 diabetes, because it is not associated with weight gain and it may promote modest weight loss. In addition, the UKPDS found that participants with obesity and type 2 diabetes who received metformin gained less weight than those on SUs (UKPDS, 1998). GLP-1 is another anti-diabetic drug that can be offered to promote or neutralise weight loss. In a six-month study, it was found that exenatide produced significant weight loss (0.9 kg)

when prescribed to patients on both metformin and SUs, suggesting a possible 2.5 kg weight loss when added to metformin (Borna, 2007).

Moreover, 27 RCTs show that GLP-1 was associated with significant weight reduction and a mean weight loss of -1.74 kg (95% CI: -3.11 to -0.48 kg) (Phung *et al*., 2010). A recent meta-analysis of 25 trials involving exenatide, administered twice daily or once weekly or liraglutide used for 20 weeks, showed there was a mean weight difference between the treatment group and control group of -2.9 kg (95% CI: -3.6 to -2.2 kg) (Kenkre *et al*., 2013). In patients with obesity and type 2 diabetes, DPP-IV inhibitors are an option for those who have failed to meet glycaemic targets with metformin alone, and they are neutral on body weight (Borna, 2007; Kenkre *et al*., 2013). A previous study of 701 patients (24 weeks) suggested no weight difference between two groups of patients on metformin alone, versus metformin plus sitagliptin (Charbonnel *et al*., 2006).

SGLT2 inhibitors have recently been approved for type 2 diabetes treatment, and are also associated with weight loss. A previous RCT of 24 weeks' duration, with dapagliflozin 2.5mg, 5 mg and 10 mg added to of metformin treatment, found a significant decrease in body weight in test subject (-2.2, -3.0 and -2.9 kg, respectively), compared with -0.9 kg in the control group (Bailey *et al*., 2010). A significant reduction in body weight was recorded in a 52-week study, in which empagliflozin was added to insulin treatment for patients who are obese with uncontrolled diabetes; the mean differences in empagliflozin 10 mg and 25 mg versus placebo were -2.39 kg (95% CI: -3.40 to -1.39 kg; p <0.001) and -2.48 kg (95% CI: -3.48 to -1.47 kg; p <0.001) (Rosenstock *et al*., 2014).

It was established in Chapter 5 (page 204) that there were differences in baseline weight associated with different prescribed anti-diabetic medications, and it was established in Chapter 3 (page 129) that baseline weight was a determinant of subsequent weight loss. Therefore, the aim of this research was to observe the effect when given anti-diabetic drugs from different categories (weight-neutral, mixed and weight-gaining oral hypoglycaemic agents) on body weight in individuals participating in the lifestyle change programme at the GCWMS. This research hypothesised that while the prescription of some anti-diabetic drugs might inhibit weight loss, some may actively enhance weight loss. Therefore, the research question posed was: are patients on weight-gaining anti-diabetic medications less likely to lose weight in the GCWMS?

6.3 Materials and methods

6.3.1 Study procedure

This intervention cohort study analysed the effect of anti-diabetic medication known to promote or inhibit weight loss for patients with type 2 diabetes and referred to the GCWMS. The same methods as described in the previous chapter were followed; i.e. using the BNF to identify the anti-diabetic drugs prescribed to participants referred to the GCWMS. Anti-diabetic medications were classified into three categories according to their effect on body weight (Chapter 5, page 198-199):

1. Weight neutral:

1a. Metformin only
1b. Metformin +DPP-IV +/OR GLP-1 +/OR SGL2

2. Mixed:

2a. **(SUs)** AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2)
2b. **(TDZs + SUs) OR (TZDs)** AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2)

3. Weight gaining:

3a. SUs only
3b. SUs + TDZs
3c. Any combination including insulin

6.3.2 Inclusion and exclusion criteria

Participants of both sexes with type 2 diabetes, aged ≥18 years and attending ≥2 sessions in the lifestyle phase were included. The reason for including only those who attended the lifestyle phase was to avoid any additional effects from the anti-obesity agents that might also be used in the phase 2 treatment of the GCWMS programme. The lifestyle phase included a combination of diet (600 kcal/day deficit diet), exercise, and behavioural changes over a 16-week period. Individuals not on oral hypoglycaemia drugs and patients on insulin only or any combination not prescribed above were excluded.

6.3.3 Statistical methods

The results were reported as a number, percentage, mean weight change, confidence intervals, 5 kg and 5% weight loss for all patients (n =998) and for subgroups of individuals who had completed the lifestyle phase by attending (≥7 sessions) over 16 weeks. These were applied to the three categories and each subgroup. Differences in mean weight change and mean percentage weight change were analysed using the t-test (between two groups) and ANOVA (more than two groups) for continuous data. The Bonferroni (pairwise) test was used to adjust for multiple comparisons. Statistical significant was defined as p <0.05, and all statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas). Finally, to minimise the effect of potential confounding factors, such as initial BMI, sex and age, a stratified analysis was used.

6.4 Results

Of the 3,063 participants included in the previous chapter, 998 patients with type 2 diabetes attended the lifestyle phase of the GCWMS, between 2008 and 2014, were included in the study. Further, 459 (46%), 412 (41.3%) and 127 (12.7%) patients were on weight-neutral, mixed and weight-gaining anti-diabetic drugs, and 49.5% of the participants were women, 40.5% were men and their mean age was 55.2 years. The mean BMIs and weights at baseline for individuals using weight-neutral, mixed and weight-gaining drugs were 42.5, 41.4 and 40.6 kg/m^2 and 116, 114.2 and 112.3 kg, respectively.

6.4.1 The association between anti-diabetic drug groups prescribing and weight change

Table 6-1 shows the mean weight change for patients on metformin only (weight-neutral, group 1a) was -3.3 kg (95% CI: -3.8 to –2.9 kg), and it was -2.5 kg (95% CI: -3.8 to -1.3 kg) for those on group 1b (weight-neutral). On the other hand, the mean weight change for the 257 patients who were on mixed drugs (group 2a) was -3.4 kg (95% CI: -3.9 to -2.9 kg) and 27% lost ≥5 kg. Similarly, 24.5% out of 155 patients in taking mixed drugs (group 2b) lost ≥5 kg with a mean weight change of -2.7 kg (95% CI: -3.4 to -2.1kg). The effects of SUs alone (weight-gaining, group 3a) on body weight found that 27.5% of the 40 patients in this group lost ≥5 kg and the mean weight change was -2.3 kg (95% CI: -3.9 to -0.7 kg); while there was a reduction of 2.9 kg (95% CI: -4.6 to -1.2 kg) in the body weight of 18 patients who took SUs + TZDs (weight gain, group 3b) and 27.5% lost ≥5 kg. The results further show that the 69 patients who used insulin with oral hypoglycaemic drugs (weight gaining, group 3c) lost 2.5 kg (95% CI: -3.3 to -1.68 kg) and 24.5% achieved their target of 5 kg weight loss. In relation to the 5% weight loss, Table 6-1 shows 30% and 27.5% of all patients in groups 3a and 3b, respectively, achieved a 5% weight loss, and these percentages were higher than weight loss percentage for the other groups.

Group	N	%	Mean weight change and 95% CI (kg)	Lost ≥5 kg	Lost≥5%
1a. Metformin					
Completers (≥7 sessions)	226	53.5	-5.0 (-5.6 to -4.3)	106 (47%)	84 (37%)
Non-completers (<7 sessions)	196	46.4	-1.4 (-1.9 to -1.0)	17 (8.5%)	11(5.6%)
Total (≥2 sessions)	423		-3.3 (-3.8 to -2.9)	123 (29%)	95 (22.5%)
1b. Metformin +DPP-IV +/OR GLP-1 +/OR SGL					
Completers (≥7 sessions)	22	61.1	-3.6 (-5.4 to -1.8)	7 (32%)	5 (22.5%)
Non-completers (<7 sessions)	14	38.8	-0.8 (-2.3 to 0.5)	1 (7%)	1 (7%)
Total (≥2 sessions)	36		-2.5 (-3.8 to -1.3)	8 (22%)	6 (16.5%)
2a. (SU) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2)					
Completers (≥7 sessions)	145	56.4	-4.6 (-5.2 to -4.0)	59 (40.5%)	56 (38.5%)
Non-completers (<7 sessions)	112	43.5	-2.0 (-2.6 to -1.3)	11 (10%)	10 (9%)
Total (≥2 sessions)	257		-3.4 (-3.9 to -2.9)	70 (27%)	66 (25.5%)
2b. (TZD +/OR SU) AND (Metformin +/OR DPP-IV +/OR GLP-1 +/OR SGLT2)					
Completers (≥7 sessions)	91	59.7	-3.8 (-4.7 to -2.9)	29 (32%)	18 (45%)
Non-completers (<7 sessions)	64	40.3	-1.2 (-1.9 to -0.5)	4 (6.0%)	3 (5.0%)
Total (≥2 sessions)	155		-2.7 (-3.4 to -2.1)	38 (24.5%)	32 (20.5%)
3a SU only					
Completers (≥7 sessions)	22	55	-3.9 (-6.1 to -1.6)	7 (32%)	8 (36.5%)
Non-completers (<7 sessions)	18	45	-0.3 (-2.6 to 1.8)	4 (22%)	4 (22%)
Total (≥2 sessions)	40		-2.3 (-3.9 to -0.7)	11 (27.5%)	12 (30%)
3b. SU + TZD					
Completers (≥7 sessions)	13	72.2	-3.3 (-5.5 to -1.2)	4 (30.5%)	4 (30.5%)
Non-completers (< 7 sessions)	5	27.7	-1.6 (-5.2 to 1.8)	1 (20%)	1 (20%)
Total (≥2 sessions)	18		-2.9 (-4.6 to -1.2)	5 (27.5%)	5 (27.5%)
3c. Any combination including insulin					
Completers (≥7 sessions)	41	58.4	-3.1 (-4.1 to -2.1)	18 (34.5%)	14 (27%)
Non-completers (<7 sessions)	28	41.5	-1.6 (-3.0 to -0.1)	4 (11%)	4 (11%)
Total (≥2 sessions)	69		-2.5 (-3.3 to -1.68)	22 (24.5%)	18 (20%)

Table 6-1 Weight loss outcomes at the end of lifestyle phase for patients with diabetes on one of the seven groups of anti-diabetic drugs.

6.4.2 The association between anti-diabetic drug prescribing and weight change, by category

6.4.2.1 Mean weight change and mean % weight loss

Seven groups were combined into three drug categories depending on the effects reported on their body weights: weight-neutral, mixed and weight-gaining anti-diabetic drugs (**Table 6-2**). Patients on the weight-neutral drugs lost more weight than those on the weight-gaining drugs by the end of the lifestyle treatment phase (16 weeks); mean weight change was (-3.3 kg, 95% CI: -3.8 to -2.9 kg and -2.5 kg, 95% CI: -3.2 to -1.8 kg, *p* =0.05), respectively (**Figure 6-1**). The statistical test lies on the borderline, but shows a significant clinical difference. However, there was no statistically significant difference between the two categories in terms of the percentage weight change, as the *p*-value = 0.17. There were no significant differences between the patients on weight-neutral drugs and those on mixed drugs in terms of mean weight change or percentage weight loss, as the total mean weight change in the mixed drugs category was -3.2 kg (95% CI: -3.5 to -2.8 kg) and the mean percentage weight loss was -2.8% for both categories. The lowest mean percentage weight loss occurred in patients using weight-gaining anti-diabetic agents; the mean percentage weight loss was -2.3%, but this was not significantly different to that of patients in the other drug categories (**Figure 6-2**).

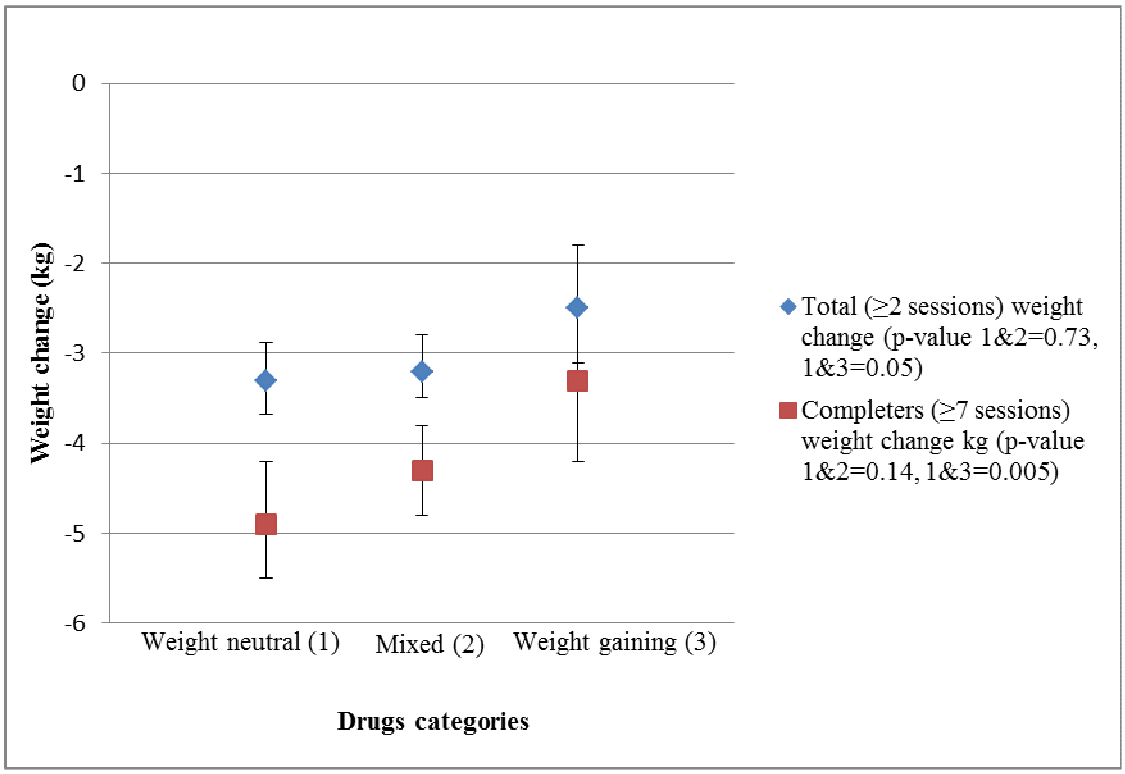

Figure 6-1 The mean weight change (kg) and the 95% confidence intervals at the end of lifestyle phase for all patients and completers on three different anti-diabetic drug categories.

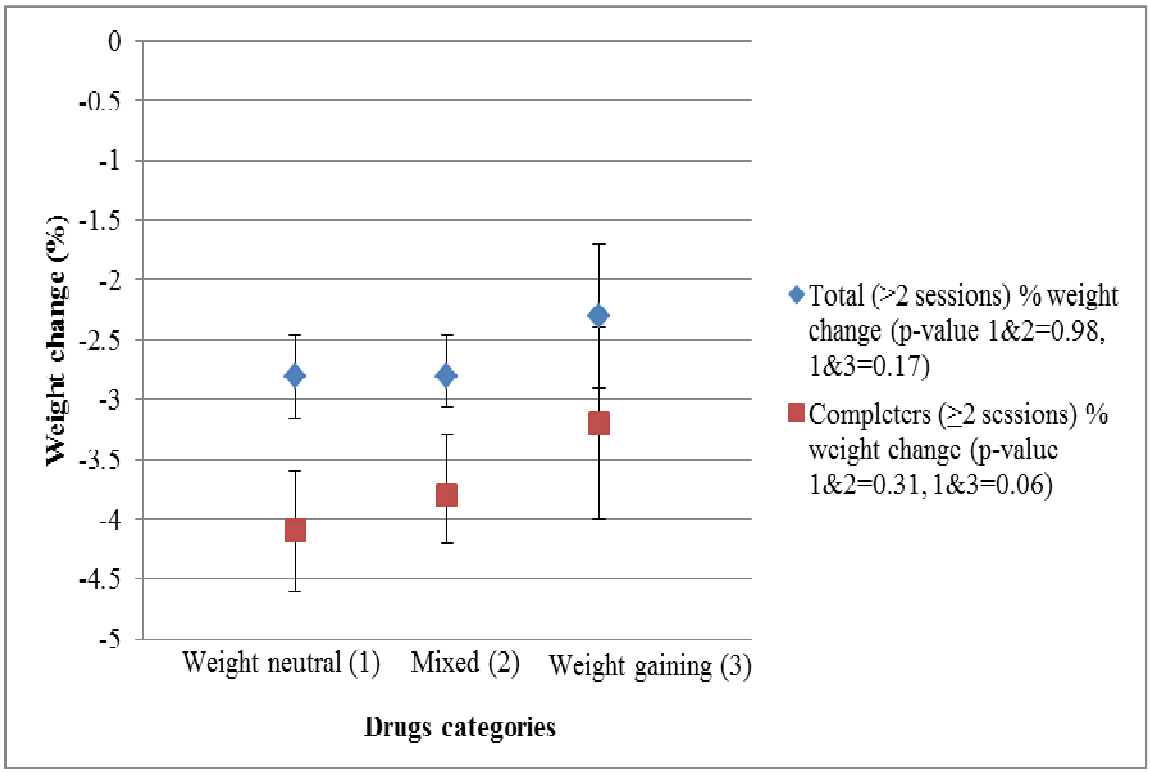

Figure 6-2 The percentage weight change (%) and 95% confidence intervals at the end of lifestyle phase for all patients and completers on three different anti-diabetic drug categories.

6.4.2.2 Target weight loss (5 kg and 5%)

With regard to target weight loss, 28.5% of the individuals using weight-neutral drugs had lost ≥5 kg, whereas 26% and 26.5% of subjects on mixed and weight-gaining drugs lost ≥5 kg, respectively. In total, 24.5% of patients on weight-gaining anti-diabetic drugs lost 5% or more, while 22% and 23.5% of patients lost ≥5% when they took weight-neutral and mixed drugs, respectively (as seen in Table 6-2, which presents weight losses of 5% or more).

Drugs categories	N (Total =998)	%	Mean weight change and 95% CI (kg)	*p*-value (total)	*p*-value (completers)	Mean % weight change and 95% CI	*p*-value (total)	*p*-value (completers)	Lost ≥5 kg	Lost ≥5%
1- Weight-neutral drugs										
Completers (≥7 sessions)	248	54.0	-4.9 (-5.5 to -4.2)			-4.1 (-4.6 to -3.6)			113 (45.5%)	89 (36%)
Non-completers (<7 sessions)	211	46.0	-1.4 (-1.8 to -1.0)						18 (8.5%)	12(5.5%)
Total (≥2 sessions)	459		-3.3 (-3.8 to -2.9)	1&2 **0.73**	1&2 **0.14**	-2.8 (-3.1 to -2.5)	1&2 **0.98**	1&2 **0.31**	131 (28.5%)	101 (22%)
2- Mixed drugs										
Completers (≥7 sessions)	236	57.2	-4.3 (-4.8 to -3.8)			3.8 (-4.2 to -3.3)			93 (39.0%)	85 (36.0%)
Non-completers (<7 sessions)	176	42.7	-1.7 (-2.2 to 1.2)						15 (8.5%)	13 (7.0%)
Total (≥2 sessions)	412		-3.2 (-3.5 to -2.8)			-2.8 (-3.1 to -2.4)			108(26%)	98 (23.5%)
3- Weight-gaining drugs				1&3 **0.05**	1&3 **0.005**		1&3 **0.17**	1&3 **0.06**		
Completers (≥7 sessions)	76	59.8	-3.3 (-4.2 to -2.5)			-3.2 (-4.0 to -2.4)			25 (33%)	22 (29%)
Non-completers (<7 sessions)	51	40.1	-1.1 (-2.2 to -0.9)						9 (17.5%)	9 (17.5%)
Total (≥2 sessions)	127		-2.5 (-3.2 to -1.8)			-2.3 (-2.9 to -1.7)			34 (26.5%)	31(24.5%)

Table 6-2 Weight loss outcomes for patients with type 2 diabetes receiving different categories of anti-diabetic drug. *P*-values were determined using t-test (*p*-value <0.05 considered statistically significant) (N: Number; CI: Confidence Interval).

6.4.2.3 Weight change outcomes for the completers

Patients who completed the lifestyle phase of the programme by attending seven sessions or more, lost the most weight across all three groups. Patients on weight-neutral drugs and those who had completed the programme lost more weight than the patients on weight-gaining drugs. The mean weight changes ranged from -4.9 kg (95% CI: -5.5 to -4.2 kg) and -3.3 kg (95% CI: -4.2 to -2.5 kg, p =0.005), respectively (Table 6-2). On the other hand, there was no significant difference between the two groups in terms of their percentage weight loss as a p-value =0.06; the mean percentage weight loss in the weight-neutral and weight-gaining groups was 4.1% and 3.2%, respectively. Overall, the mean percentage weight loss was not significantly different among the three different drug categories. Patients on mixed drugs lost -4.3 kg (95% CI: -4.8 to -3.8 kg), which is equivalent to 3.8% weight loss. Among the 248 patients with type 2 diabetes (on weight-neutral drugs) who completed the lifestyle phase, 113 (45.5%) lost at least 5 kg; meanwhile, of the 236 patients on mixed drugs, 93 (39.0%) had lost 5 kg or more. Moreover, 25 (33%) patients on weight-gaining drugs (out of the 76 who completed the programme) lost at least 5 kg. Patients on weight-gaining drugs were less likely to lose ≥5% of their body weight, when compared with the other patients in different drug categories.

6.4.3 Weight loss outcomes for subgroups

6.4.3.1 Sex

The null hypothesis is that the weight changes associated with anti-diabetic prescribing would be no different in men and women. Overall, participants who were prescribed weight-gaining anti-diabetic drugs lost less weight than those on weight-neutral drugs. The mean weight loss in individuals on weight-gaining anti-diabetic drugs was -2.5 kg (95% CI: -3.2 to -1.8 kg), compared to -3.3 kg (95% CI: -3.8 to -2.9 kg) for weight-neutral drugs, and the *p*-value was 0.05, which indicates the difference was statistically significant (Table 6-2). On the other hand, the difference between weight-neutral and mixed drugs was not statistically or clinically significant, as the mean difference was -0.1 kg and the 95% CI overlapped. Since men were more likely to be prescribed weight-gaining anti-diabetic drugs (Table 5-3) and to achieve target weight loss (Table 3-4), sex may have confounded the association between weight loss and anti-diabetic drug type.

The mean weight change for men and women using weight-neutral drugs was -3.93 kg (95% CI: -4.7 to -3.0 kg) and -2.98 kg (95% CI: -3.4 to -2.5 kg) respectively; this difference was statistically significant (p =0.02) **(Figure 6-3).** However, there was no difference between men and women in terms of the use of mixed or weight-gaining anti-diabetic drugs (**Table 6-3)**. The results show that a higher proportion of men used mixed drugs (45.4%) compared with those used weight-neutral (35.4%) or weight-gaining (43.3%) drugs, but they lost less weight than those prescribed weight-neutral medications. The mean weight change in the weight-gaining group was -2.51 kg (95% CI: -3.7 to -1.2 kg), compared with -3.93 kg (95% CI: -4.7 to -3.0 kg) and -3.32 kg (95% CI: -3.8 to -2.8 kg) in the weight-neutral and mixed drug groups, respectively.

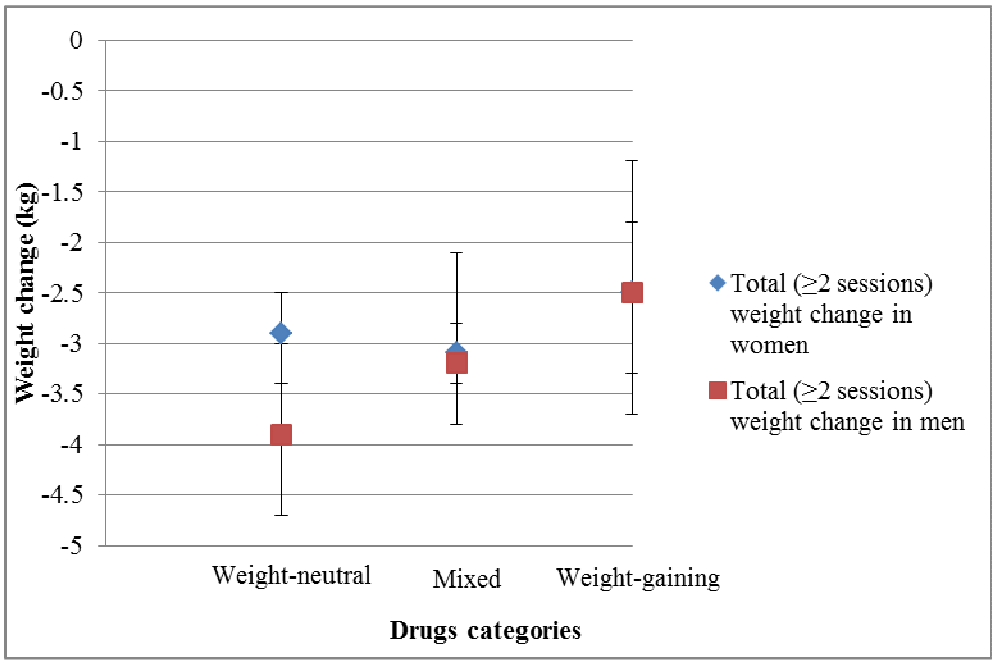

Figure 6-3 The mean weight change (kg) and the 95% confidence intervals at the end of the lifestyle phase in both sexes in three different anti-diabetic drug categories.

6.4.3.2 BMI

The null hypothesis is that the weight changes associated with anti-diabetic prescribing are no different in heavier and lighter patients. Overall, there was a linear trend between weight loss and higher BMIs in each drug category, but this relationship was not significant and the CIs overlapped **(Figure 6-4)**. In terms of initial BMI difference, those with BMI ≥50 kg/m^2 on weight-neutral drugs lost more weight than patients with BMI 30-34.9 kg/m^2. The mean weight loss was -3.98 kg (95% CI: -5.0 to -2.9 kg) and -2.48 kg (95% CI: -3.2 to -1.6 kg) respectively (Table 6-3). However, the Bonferroni test shows that the difference between these two categories was not statistically significant (p =0.35).

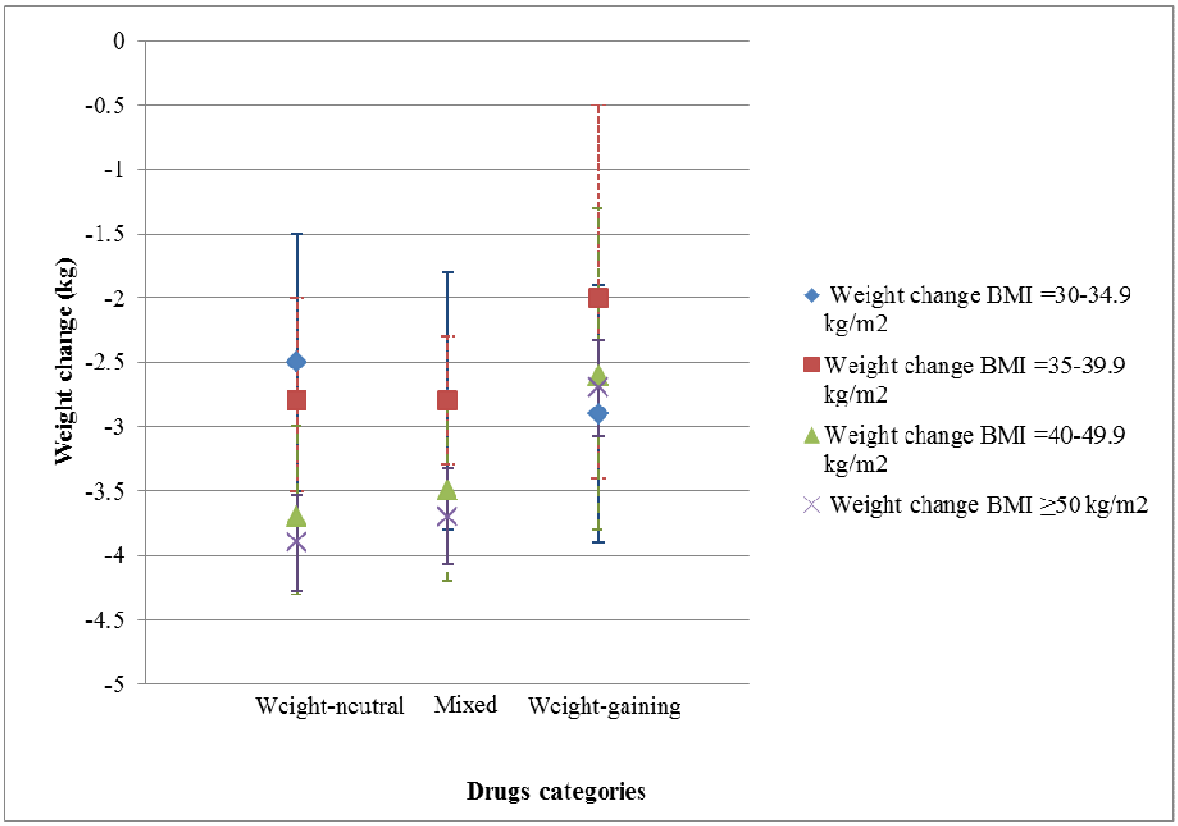

Figure 6-4 The mean weight change (kg) and the 95% confidence intervals at the end of the lifestyle phase, across different BMI categories of patients in three different anti-diabetic drug categories.

6.4.3.3 Age

The null hypothesis: the weight changes associated with anti-diabetic prescribing are no different in younger and older patients. When the overall results were split according to the age of the patients, some differences in weight changes in each of the three groups were observed, but the CIs overlapped **(Figure 6-5)**. Generally, as older people were more likely to be prescribed weight-gaining anti-diabetic drugs (Table 5-2) and to achieve target weight loss (Table 3-4), age may confound the association between weight loss and drug type. However, no statistically significant difference was found across age categories in each drugs group. The *p*-values for weight-neutral, mixed and weight-gaining drugs were 0.55, 0.44 and 0.55 respectively (Table 6-3).

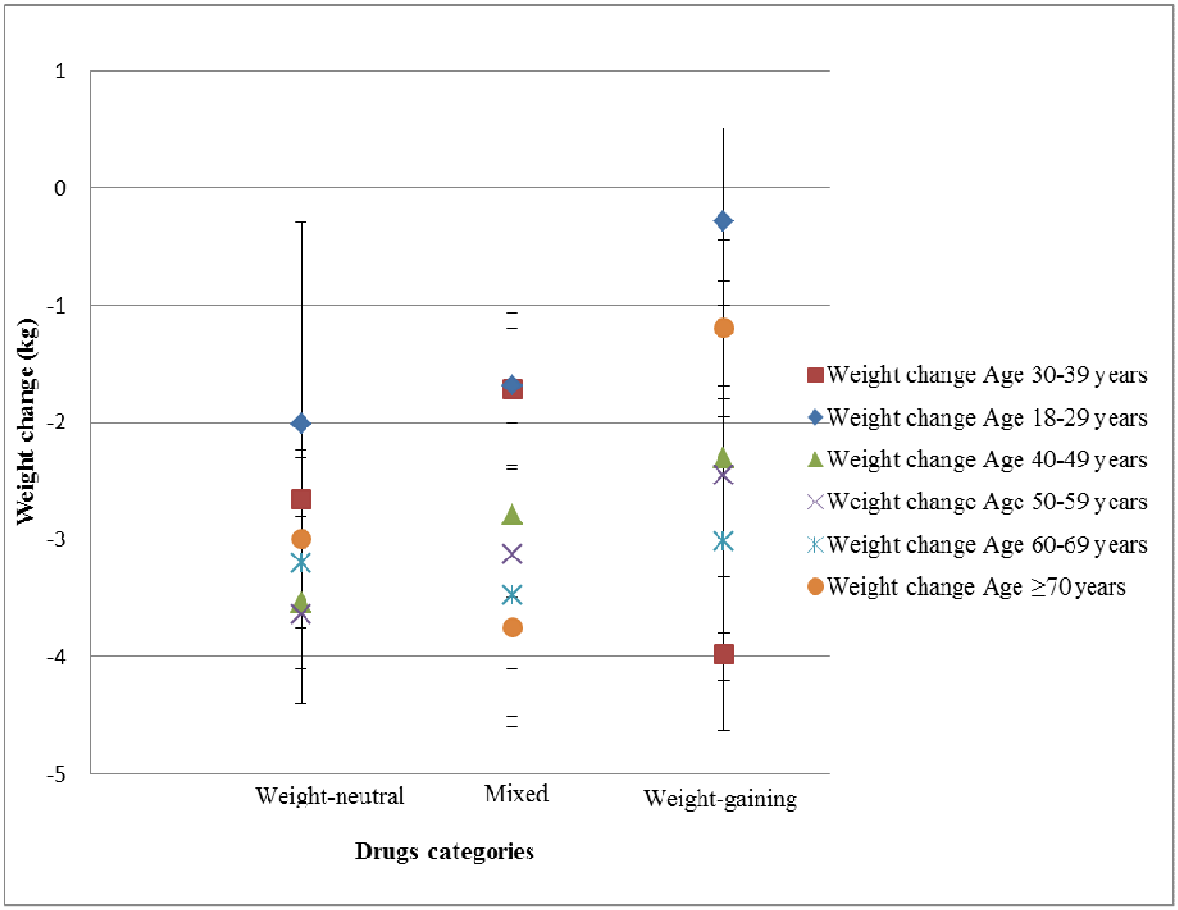

Figure 6-5 The mean weight change (kg) and the 95% confidence intervals at the end of the lifestyle phase, across different age categories of patients in three different anti-diabetic drug categories.

6.4.3.4 SIMD

The null hypothesis: the weight changes associated with anti-diabetic prescribing are no different in people with different socioeconomic statuses. In general, whilst patients in the least deprived area were more likely to achieve their target weight loss (Table 3-4), socio-economic status did not influence the prescribing of anti-diabetic drugs (Table 5-8). It might therefore be expected that SIMD may not have confounded the association between weight loss and drug type. Weight loss among those on weight-neutral, mixed or weight-gaining anti-diabetic drugs did not vary by socio-economic circumstance.

	Weight-neutral drugs (*n* =459)			Mixed-drugs (*n* =412)			Weight-gaining drugs (*n* =127)		
Category (n)	**Mean weight change (kg) and (95% CI)**	**(%)**	***P***	**Mean weight change (kg) and (95% CI)**	**(%)**	***P***	**Mean weight change (kg) and (95% CI)**	**(%)**	***P***
Male (404)	-3.93 (-4.7 to -3.0)	35.4	0.02	-3.32 (-3.8 to -2.8)	45.4	0.59	-2.51 (-3.7 to -1.2)	43.3	0.98
Female (594)	-2.98 (-3.4 to -2.5)	64.6		-3.12 (-3.6 to -2.5)	54.6		-2.50 (-3.2 to -1.7)	56.7	
BMI 30-34.9 kg/m^2 (179)	-2.48 (-3.2 to -1.6)	15.3	0.08	-2.80 (-3.4 to -2.1)	17.2	0.27	-2.86 (-3.9 to -1.7)	22.8	0.84
BMI 35-39.9 kg/m^2 (301)	-2.82 (-3.5 to -2.0)	26.4		-2.83 (-3.3 to -2.3)	31.3		-2.04 (-3.4 to -0.5)	30.7	
BMI 40-49.9 kg/m^2 (414)	-3.68 (-4.3 to -3.0)	45.7		-3.5 (-4.2 to -2.8)	41.0		-2.61 (-3.8 to -1.4)	37.8	
BMI ≥50 kg/m^2 (104)	-3.98 (-5.0 to -2.9)	12.6		-3.70 (-5.3 to -2.0)	10.4		-2.72 (-4.7 to -0.7)	8.7	
Age 18-29 years (24)	-2.01 (-3.6 to -0.3)	4.4		-1.69 (-4.6 to 1.2)	0.5		-0.29 (-1.6 to 1.0)	1.6	
30-39 years (78)	-2.66 (-3.7 to -1.6)	12.2	0.55	-1.72 (-2.8 to -0.6)	3.9	0.44	-3.98 (-6.9 to -0.9)	4.7	0.55
40-49 years (186)	-3.54 (-4.4 to -2.6)	22.9		-2.79 (-3.5 to -2.0)	15.5		-2.31 (-3.8 to -0.8)	13.4	
50-59 years (330)	-3.64 (-4.4 to -2.8)	30.9		-3.13 (-3.7 to -2.4)	36.2		-2.45 (-3.8 to -1.0)	30.7	
60-69 years (289)	-3.2 (-4.1 to -2.3)	22.9		-3.48 (-4.1 to -2.8)	33.0		-3.02 (-4.2 to -1.8)	37.8	
≥70 years (91)	-3.00 (-4.6 to -1.4)	6.7		-3.75 (-5.2 to -2.2)	10.9		-1.20 (-2.7 to 0.3)	11.8	
SIMD: 1 (most deprived) (396)	-2.92 (-3.5 to -2.2)	41.9		-3.04 (-3.6 to -2.4)	38.2		-2.71 (-3.6 to -1.7)	37.8	
2 (202)	-3.28 (-4.0 to -2.5)	21.5	0.39	-2.78 (-3.5 to -1.9)	19.0	0.45	-1.86 (-3.6 to -0.7)	20.5	0.15
3 (146)	-3.85 (-4.9 to -2.7)	14.0		-3.67 (-5.0 to -2.3)	14.6		-1.10 (-2.4 to 0.2)	17.3	
4 (124)	-3.05 (-4.5 to -1.5)	9.4		-3.1 (-4.0 to -2.2)	14.8		-3.48 (-5.2 to -1.0)	15.7	
5 (least deprived) (126)	-4.05 (-5.3 to -2.7)	13.2		-3.88 (-4.9 to -2.8)	13.4		-4.14 (-7.2 to -1.0)	8.7	

Table 6-3 Stratified analysis of weight loss with three different categories of anti-diabetic drugs at end of the lifestyle phase (*n*: number; CI: Confidence Interval).

6.5 Summary of the main findings

- The mean initial BMI at baseline was higher in the weight-neutral drug group.
- Patients on the weight-neutral anti-diabetic drugs lost more weight than the patients on weight-gaining drugs.
- There was no significant difference in terms of percentage weight loss between the three different groups; this might be attributable to the differences in initial weight between the groups.
- In terms of lifestyle programme completion, a higher proportion of patients on weight-neutral anti-diabetic medication achieved their target weight loss compared with the other groups.
- In terms of lifestyle programme completion, mean weight loss was higher in those on metformin only, and lower in those on any combination, including insulin, followed by those on SUs + TZDs.

6.6 Discussion

6.6.1 Weight loss outcomes

Previous trials have reported the effect of anti-diabetic drugs on body weight when patients are being treated by controlling their blood glucose in their normal daily life. However, this is the first study to report the effects of these drugs on the body weight of individuals with diabetes when referred to a weight management programme for obesity treatment. In other words, this study has represented the effects of anti-diabetic drugs on weight change alongside lifestyle change. The lifestyle changes implemented included a 600 kcal deficit diet, exercise, and behavioural intervention. Overall, the patients on metformin or metformin and mixed anti-diabetic drugs lost more weight than the individuals on SUs, SUs + TZDs and any drugs combination including insulin.

Those who used metformin with weight-neutral drugs (group 1b) lost less weight than those on metformin alone (group 1a), and the difference was statistically significant. The mean weight change was -2.5 kg (95% CI: -3.8 to -1.3 kg) and -3.3 kg (95% CI: -3.8 to -2.9 kg). This might be because those on one medication are usually more adherent to their medication, hence not having had their medications increased, and are possibly also more adherent to diet and physical activity compared with those taking multiple drugs. Additionally, it may be because of the different duration of diabetes, as those who had type 2 diabetes for a shorter period of time were perhaps more amenable to behaviour change than those who have lived with diabetes for several years without attempting weight loss.

In terms of using drugs that may cause weight gain, there was no difference between group 3a and group 3b in terms of ≥5 kg weight loss, as 27.5% of those in both groups lost at least 5 kg of their initial weight. In terms of the percentage weight change, there was no statistically significant difference between participants in the weight-neutral drugs category and those in the weight-gaining drugs category. This might be because the mean weight at the baseline was higher in the weight-neutral group compared with the weight-gaining group.

However, due to the low number of patients in some of these groups, the drug groups were combined into three categories depending on their effect on body weight. To our knowledge, this is the first study to target patients with diabetes and obesity enrolled in a weight management programme. Due to the uniqueness of the study, it is hard to compare

it with previous studies, because the data reported in previous studies were collected from general practices or specialised diabetes centre irrespective of BMI.

6.6.2 Comparisons with other findings

The results reported here on the effect of metformin, SUs and TZDs on body weight confirmed previous trial results, which showed that there was an association between using metformin, and stable or lower weight. Meanwhile, SUs and TZDs might cause weight gain in patients with diabetes. For instance, an earlier study (1-year duration) of 639 individuals with type 2 diabetes showed groups of patients who received SUs plus TZDs gained an average of 2.8 kg compared with a reduction of 1 kg in metformin plus SUs group (Hanefeld *et al*., 2004). In addition, a four-year randomised study of 4,360 subjects with type 2 diabetes uncontrolled by lifestyle intervention and treated with metformin, rosiglitazone or glibenclamide showed individuals in the metformin group lost weight; however, a weight gain occurred in glibenclamide and rosiglitazone groups, but this was most significant in rosiglitazone group when compared with either of the other groups (Kahn *et al*., 2006). Moreover, a retrospective study (1-year duration) of 2,641 participants reported that patients on metformin had lost an average weight of -2.6 kg (95% CI: -2.5 to -2.9 kg), and those on SUs had gained 0.3 kg (95% CI: -0.2 to 0.8 kg); a result consistent with the current findings (Kostev *et al*., 2015).

The reason for the effects of metformin on body weight is that it might influence body fat distribution in people with type 2 diabetes (Golay, 2008). A randomised study of 26 weeks' duration reported metformin significantly decreased visceral fat mass compared with placebo, whereas rosiglitazone did not (Hallsten *et al*., 2002). DPP-1V and GLP-1 in combination with metformin resulted in weight loss or weight remaining neutral, compared with SUs or TZDs; which agrees with the results of a previous study, irrespective of study duration (Phung *et al*., 2010).

6.6.3 Lifestyle programme completion

There was no significant variation in completion status between patients and drug category, as the percentage range for the three categories was from 54% to 59%. This research found that the total and completer patients who are diabetic on weight-neutral drugs lost more weight than the patients on weight-gaining anti-diabetic drugs, and there was no difference with those on mixed drugs. This might be because of the effects of these

drug categories on body weight or due to the effects of other factors, such as initial BMI or patient age. At baseline, this research showed that patients on weight-gaining drugs were older and weighed less than individuals on weight-neutral drugs. Findings reported in Chapter 3 and a study by Morrison *et al.* (2011) that evaluated the lifestyle phase of the GCWMS programme, showed that heavier and older people are more likely to lose their target weight. Generally, as the participants in the weight-neutral group were heavier and younger than the patients in the weight-gaining drugs group, it could be concluded that the main reason they lost more weight could be due to the effect of the drugs on body weight in addition to other factors.

Earlier studies have reported that men and women vary in their behaviour and attitudes toward their diabetes. For instance, Nothwehr and Stump (2000) suggested that women were more likely to follow a diet to control blood glucose, but undertook less physical activity than men. However, the current results show that the relationship between anti-diabetic drugs and weight change was not confounded by sex. Based on these results, men were the most represented in the mixed drugs group (45.4%). It might therefore be expected that this group would lose the most weight if the drugs themselves had no effect, and that the patients' sex was entirely confounding the relationship. Another example was that as women accounted for the highest proportion of people in the weight-neutral drugs group (64.6%), this group might have been expected to lose lowest amount of weight. However, the lowest proportion of men was in the weight-neutral drugs group, and they lost the largest amount of weight. The null hypothesis can therefore be accepted, making it likely that the relationship between drug type and weight loss was not confounded by sex.

A previous 26-week RCT compared the effect of liraglutide or rosiglitazone with glimepiride on weight change and glycaemic control in 1,041 participants. It reported that sex does not influence the effect of liraglutide on weight change, which is consistent with the current results (Marre *et al*., 2009). In addition, in a two-year follow up of the DiaRegis cohort study, Hartmann *et al*. (2015) found that the association between anti-diabetic drugs and weight change was not influenced by the sex or patient age.

In terms of BMI factor, the results show that there was a strong linear relationship between weight loss and BMI, although this relationship was not statistically significant. These results are in agreement with Ji *et al*. (2013), who showed that baseline BMI had no effect on weight change in Chinese patients with type 2 diabetes who used metformin. In

addition, the results show that there was no statistically significant difference between the age categories in terms of mean weight change. Therefore, it might be possible to accept the null hypothesis; the results confirm that age and BMI did not confound the relationship between anti-diabetic drugs prescribing and weight loss.

In terms of socio-economic status, a higher proportion of patients from the most affluent areas were on weight-neutral drugs (13.1%), compared to those on weight-gaining drugs (8.6%). However, they lost almost the same amount of weight -4.05 kg (95% CI: -5.3 to -2.7 kg) and -4.14 kg (95% CI: -7.2 to -1.0 kg). It may thus be concluded that the association between weight change and drug type was not confounded by SIMD.

6.6.4 Target weight loss

In terms of achievement of target weight loss (≥5 kg) in the weight-gaining drug categories, there were modest differences in the percentages of patients losing 5 kg or more, and between the total number of patients and the completers, as the difference was just 6.5% compared with the other groups. This indicates that patients in this category gained some weight during the weight management programme; this might be a consequence of the effects of drugs such as SUs, TZDs and insulin. The majority of the patients in the mixed and weight-gaining drug categories who lost ≥5 kg, lost ≥5% of their body weight, compared with patients who used weight-neutral anti-diabetic drugs. This might be due to their higher initial weight and the BMI in the weight neutral-drugs group compared with the other groups.

6.6.5 Recommendation

Despite there are beneficial effects of weight loss on glycaemic control and reducing cardiovascular risk in people with diabetes, weight gain seems to be a barrier to controlling blood glucose, and is commonly associated with the use of some anti-diabetic drugs. This might cause patients to become discouraged from adhering to their treatment. Therefore, physicians should consider the weight effects of anti-diabetic drugs when managing patients with obesity and type 2 diabetes, so that they can offer them weight-neutral anti-diabetic drugs that will supplement the patient's need to embark upon a healthier lifestyle. In general, patients with obesity and diabetes have greater difficulty losing weight than people without diabetes (Wing *et al*., 1987), and many anti-diabetic drugs are associated with weight gain. Therefore, patients should be encouraged to enrol in a weight

management programme to achieve their glycaemic and weight targets, and attempts should be made to provide patients with alternative medications that are not associated with weight gain, or to reduce these agents without compromising glycaemic control.

6.7 Strengths and limitations

A key strength of the present study was that it is the first research to observe the effects of anti-diabetic drugs on weight change among participants with type 2 diabetes referred to attend a lifestyle weight management programme. This intervention cohort study, which has quite a large sample size, reported the mean weight loss and the mean percentage weight loss, which provides a comprehensive data set and powerful results. Use of the GCWMS provided a good sample of individuals with diabetes from different demographics, all of whom were referred for obesity management.

Notable limitations of the research include information bias, as each anti-diabetic drug category was classified into specific groups; and some anti-diabetic groups were not included. Therefore, this might have reduced the observed association. Another weakness of the study was that the data did not provide information regarding the patients' duration of type 2 diabetes, or how long they had used other drugs to the study, both of which may influence or decrease the efficacy of some drug classes. Moreover, there was no information about the doses of anti-diabetic drugs prescribed to the patients. One source of weakness in this research, and one which could have affected the anti-diabetic drugs effect on weight change was the short duration of study, as outcomes were reported after the lifestyle phase (16 weeks). Therefore, a further study could be undertaken to assess the long-term effects of anti-diabetic medication on weight change.

6.8 Research implications

In conclusion, due to the lack of evidence from other sources investigating the effect of anti-diabetic drugs on weight change among patients enrolled in a weight management programme, it is not possible to compare the results of this research with earlier empirical findings. The ADA recommended an anti-diabetic drug for type 2 diabetes with the ability to reduce hyperglycaemia, while the SIGN guidelines reported a clear treatment plan for patients with obesity and type 2 diabetes. Based on the above, and because many patients with type 2 diabetes are overweight or obese, there may be good reasons why GPs prescribed weight-gaining drugs. However, it may be possible to improve weight loss by optimising anti-diabetic drug prescribing. Further research, possibly of a qualitative nature, would be needed to determine whether there is scope to change anti-diabetic drug prescribing. Further analysis using multi-variable regression was considered, but it was found that a regression model cannot easily be fitted to change measures and there was no simple approach that could have been used to achieve this (Chiolero *et al*., 2013). In future investigations, it might be possible to test the association between weight loss and reductions in the doses of certain medications, such as the hypoglycaemic agents and anti-hypertensive drugs. Further implications will be discussed in the following chapter.

Chapter 7: Conclusion

7.1 Relationship between thesis chapters

One of the risk factors for the development of diabetes mellitus is obesity. While weight loss can be achieved through lifestyles modifications, numerous RCTs have demonstrated that the additional use of orlistat, the only drug licensed in the UK specifically for the treatment of obesity, can increase this benefit. One such RCT was a two-year study supported by La Roche (O'Meara *et al*., 2001); others were considered in a HTA report. In 2010, the SIGN guidelines recommended that the drug could be used in weight loss management as an adjunct to lifestyle interventions. The impact of orlistat on patients with obesity in terms of diabetic outcomes, including FPG and HbA1c, has been examined in medium- and small-scale research studies. A further example of the approved clinical use of orlistat is in the GCWMS, where the drug can be employed within the multidisciplinary weight management programme. Chapter 2 therefore comprised a systematic review of the impact of the use of orlistat in the management of patients who are overweight or obese in terms of their glycaemic values, along with a meta-analysis of the literature.

In the United Kingdom, there are typically four tiers of weight management services programmes. Two of these are tier 2 services (lifestyle interventions) and tier 3 services (specialist weight management programmes). The NICE has identified four main gaps in the literature concerning these programmes (NICE, 2014). Firstly, there have been insufficient trials that directly compare different lifestyle weight management programmes in the United Kingdom. Secondly, small sample sizes and temporally restricted data collection points limit the usefulness of existing evidence. The third limitation is inadequate evidence regarding the relative efficacies of different interventions in terms of weight loss. Finally, the effectiveness of weight loss programmes varies according to socioeconomic group, gender and age; insufficient evidence exists regarding this.

Based on the above, GCWMS referrals over the period from 2008 to 2014 were considered in Chapter 3, to investigate the impact on weight loss of lifestyle intervention (phase 1). The influence of diabetes status, age, the SIMD, initial BMI and sex were considered for this large sample size. Chapter 4 examined the efficacy of a range of interventions on weight loss, for example, LCD, FWL and orlistat (phase 2) for these patients.

Finally, Chapter 3 demonstrated that there was a significant difference in terms of weight loss between patients with and without diabetes who were referred to the GCWMS. Additionally, a wide range of RCTs have reported that some anti-diabetic drugs might have

weight-neutral or weight-loss effect, whilst some may cause weight gain without any correlation with BMI. As the SIGN guidelines of 2010 set out a treatment plan for patients who are overweight or obese with type 2 diabetes, investigation of the commitment of GPs to prescribing hypoglycaemic agents prior to referral to weight management services was necessary. Therefore, in Chapter 5, the pattern of prescribing anti-diabetic drugs to patients referred to the GCWMS was studied. Following on from this, Chapter 6 described the impact of different classes of anti-diabetic drugs on weight loss.

7.2 Review of principal findings

This thesis evaluated the effectiveness of GCWMS on obesity treatment, and reviewed the impact of the anti-obesity drug orlistat on glycaemic control in patients with obesity and type 2 diabetes. The prescribing patterns for anti-diabetic drugs were investigated and their effect on weight loss observed.

Chapter 2 presented a systematic review and meta-analysis, demonstrating that a regime of orlistat 120 mg three times per day, in association with lifestyle intervention resulted in greater glycaemic control and significantly improved weight loss than was possible with lifestyle interventions alone. In the first three months of orlistat use, reductions were seen in FPG and HbA1c; moderate rises were also subsequently observed, despite weight loss continuing for up to one year. Neither weight loss nor glycaemic value were conclusively found to be affected by the combination of physical activity and a placebo, as insufficient studies using this regime were available.

Fewer than half of the patients completing the lifestyle phase of the GCWMS in the cohort studies examined in Chapters 3 and 4 achieved a weight loss of 5 kg. It was found that those most likely to finish the programme and achieve the target weight loss were male, older, lived in more affluent areas, had higher BMIs, and without diabetes. Approximately 50% of the participants had lost 5% or more of their initial weight, and approximately 55% had lost at least 5 kg by the end of phase 2. Those patients who performed well were selected to proceed to the FWL programme; approximately six out of seven of these achieved their target weight loss. While the patients using orlistat successfully lost weight, only 30% achieved their target weight loss. The intervention found to be least effective was LCD, with fewer than one-quarter of patients achieving their target losses.

Approximately half the patients in the cross-sectional study described in Chapter 5 were prescribed weight-neutral anti-diabetic drugs. However, comparing 2008 and 2014, i.e. following the publication of the SIGN guidelines in 2010, there was no change in the pattern of prescribing drugs triggering a decrease in weight. The least frequently prescribed medication was SUs plus TZDs; the most commonly prescribed was metformin. Furthermore, the study revealed that other confounding factors might have influenced the prescription of anti-diabetic drugs; these were BMI at the outset and age.

Chapter 6 described an intervention cohort study. It was observed that, while not statistically significant, there was a clinically significant improvement in weight loss among the GCWMS patients on weight-neutral anti-diabetic medication compared to those on weight-gaining anti-diabetic drugs. However, there was no significant difference in terms of percentage weight loss. A potential reason for this is that the former patients' initial weights were higher than those of the latter group. A total of 30.5% of patients completing the programme on the SUs plus TZDs regimen achieved their target weight loss; for the metformin group, this figure rose to nearly half of all patients (47%).

7.3 Strengths and limitations

Each individual chapter of this thesis has discussed the strengths and limitations of the respective studies. Therefore, this section considers those associated with the overall methodology used throughout the research, which, as has been seen, comprised five studies – a systematic review and an associated meta-analysis, as well as a cross-sectional study and prospective cohort studies.

The systematic review and meta-analysis were performed in accordance with the Cochrane methodology and reported according to PRISMA guidelines. The review included RCTs and assessed the impact of physical activity and of placebo, evaluating two forms of intervention. However, it only considered literature concerning patients who are overweight or obese with type 2 diabetes. Evidence of significant bias was assessed in accordance with the guidelines of the Cochrane Collaboration and no significant bias was found. Further use of the guidelines in terms of the I^2 statistic investigated consistency in the studies' results. This identified the statistic expressing the proportion of inconsistency (quantified as a percentage) that cannot be accounted for by random probability or sampling error alone (Higgins *et al.*, 2003). Analysis using this parameter produces a readily quantifiable and interpretable measure of inconsistency, with an associated uncertainty level that is independent of sample size. The values of I^2 can be interpreted across four broad ranges: 'Considerable heterogeneity' (I^2 =75-100%), 'Substantial heterogeneity' (I^2 =50-90%, 'Moderate heterogeneity' (I^2 =30-60%) and 'Might not be important' (I^2 =0-40%). The current results show a considerable heterogeneity between studies that reported the HbA1c and FPG outcomes. The overall I^2 between the studies that reported the HbA1c and FPG outcomes was (100%, p =0.001 and 97.4%, p =0.001, respectively). In addition, there was substantial heterogeneity between the studies that reported the weight change (I^2 =76.6%, p =0.001), except for the studies that reported the weight change after three months.

Therefore, further research might be needed to examine the effect of orlistat on glycaemic control in real life for patients with obesity and type 2 diabetes. In the systematic review of RCTs, orlistat can result in adverse gastrointestinal reactions; as the participants in the research – both patients and study personnel – might have been influenced by the presence of such reactions, as they could have inferred whether or not a placebo had been administered.

There are a large number of factors that can influence the pattern of prescribing medication for patients with type 2 diabetes. This thesis is the first to investigate such a pattern for anti-diabetic medication used by patients referred to a weight management programme, and benefitted from the large sample size offered by the GCWMS. The thesis is also the first to observe the effect of the anti-diabetic drugs on weight loss. The resultant dataset incorporated patients from a wide range of socio-economic backgrounds and enabled impact of this programme to be examined with respect to patients' age, BMI, SIMD and sex. While the research was stratified for many such potential confounding factors, residual ones remain possible in any observational studies of this nature.

A range of sources of missing data resulted in some limitations in the study, which also reduced the variables available in the evaluation of the phase 3 maintenance phase. As this was a prospective study that included all patients referred to the GCWMS, it is likely that selection bias was almost certainly not present in the cross-sectional study. However, information bias may have been present as real-world clinical data were used. Attrition bias and information bias may have occurred in the cohort studies. Some patients did drop out of the GCWMS, but data explaining the reasons for this were not available. Inadequate data regarding the doses of anti-diabetic drugs used both before and after the lifestyle intervention programme prevented exploration of the impact of weight loss on the prescription of the dose of hypoglycaemic drugs.

7.4. Research in relation to other findings

In this section, the results of the research as reported in the preceding chapters were highlighted and compared to other important research areas.

In this research, the systematic review and meta-analysis of RCTs showed orlistat is an effective treatment for improving glycaemic control in people who are overweight or obese with type 2 diabetes, when used as an adjunct to lifestyle interventions. This is consistent with the results of the Cochrane review (Padwal *et al*., 2004), which reviewed patients both with and without diabetes. It also included an analysis of a subgroup of patients, reporting outcomes only for patients with diabetes. In that review of five studies, the mean HbA1c and FPG were -4.15 mmol/mol (95% CI: -6.44 to -1.96 mmol/mol) and -1.03 mmol/l (95% CI: -1.49 to -0.57 mmol/l) after one year. Three of these studies were included in the current review (Berne *et al*., 2005; Kelley *et al*., 2002; Miles *et al*., 2002), and the results reported were similar. The mean differences in HbA1c and FPG were –5.29 mmol/mol (95% CI: -7.31 to -3.27 mmol/mol) and -1.06 mmol/l (95% CI: -1.44 to -0.68 mmol/l) respectively.

The respective mean differences in HbA1c and FPG between orlistat and the control group in another systematic review (Avenell *et al*., 2004) of six studies were -1.85 mmol/mol (95% CI: -2.62 to -1.09 mmol/mol) and -0.24 mmol/l (95% CI: -0.34 to 0.14 mmol/l). Therefore, the finding of this thesis that glycaemic control is promoted by orlistat is supported by these findings, although the review of Avenell *et al*. (2004) included only trials with follow-ups at one year and involving patients with and without type 2 diabetes.

A systematic review in an HTA report (O'Meara *et al*., 2001) also investigated the effect of orlistat on weight loss, comparing the loss in a group prescribed orlistat with that in a control group. It reported that the trial groups achieved mean weight changes of -1.24 kg (95% CI: -2.6 to -0.1 kg), -3.41 kg and -2.9 kg (95% CI: -3.6 to -2.1 kg) after three months (two studies), six months (two studies) and one year (four studies) respectively. The research reported in this thesis also showed lower mean weight differences at 6 and 12 months (the mean weight difference at 6 and 12 months was -2.23 kg (95% CI: -2.73 to -1.74 kg) and -2.64 kg (95% CI: -3.09 to -2.19 kg) respectively; a potential reason for this might be the inclusion of participants both with and without diabetes. However, at three months, the thesis results showed greater weight changes (-1.73 kg (95% CI: -2.12 to -1.34

kg)) as the patients were using 120 mg of orlistat rather than the 50-60 mg prescribed in the review study.

Similar results were found in the previous two studies evaluating the GCWMS (Morrison *et al*., 2011; Logue *et al*., 2014) and Chapters 3 and 4 of this thesis – that is, the lifestyle intervention of the NHS GCWMS led to effective weight loss, albeit for less than half of the patients completing the programme. The weight losses achieved were comparable with other NHS Tier 3 weight management programmes, such as SLiM (Brown *et al*., 2015) and the FWMS (Jennings *et al*., 2014). Similar commercial programmes, such as WMOR (Birnie *et al*., 2016), Slimming World, Rosemary Conley and Counterweight (The Counterweight Project Team, 2008) also produced similar results. However, 33% of patients on the Weight Watchers programme lost at least 5% of their initial weight (Ahern *et al*., 2011), compared to 25.5% of GCWMS patients, representing a higher success rate.

Chapter 5 also showed consistency with previous studies. Patients with lower BMIs were more likely to be prescribed drugs associated with weight gain, such as TZDs or SUs, while patients with higher BMIs were more likely to be given weight-neutral drugs such as metformin. A previous study reported that for patients on SUs, the percentages with BMIs of <25, 25-<30, 30-<35 and ≥35 kg/m^2 were 36.6%, 30.6%, 26.3% and 27.4% respectively; the corresponding proportions of patients prescribed metformin were 74.6%, 83.5%, 84.5% and 86.9% (*p*-value <0.001) respectively (Hartmann *et al*., 2015). A previous study with a large (*n* =57,518) dataset reported that 90% of patients were prescribed metformin. This is consistent with this research, in which metformin was the most frequently prescribed anti-diabetic medication, while TZDs and SUs were the least frequently prescribed. According to primary care data in the United Kingdom, between 2009 and 2013, 0.1% and 7.9% of patients were prescribed TZDs and SUs respectively (Sharma *et al*., 2016). This research was also in line with the results of a previous study, which found a connection between the prescribing of anti-diabetic medications and sex, initial BMI and age (Kamrai & Sachdeva, 2010).

Chapter 6 described the first piece of research investigating the effect of anti-diabetic medication on weight change for patients with obesity who were referred to a weight management service. Therefore, any comparison with previous findings is difficult. However, the results were broadly in agreement with previous trials that determined that GLP-1, metformin and DDP-4 inhibitor were all associated with weight loss in type 2 diabetics (Kostev *et al*., 2015; Phung *et al*., 2010). They also supported another review

study (Krentz and Bailey, 2005), systematic reviews and meta-analyses (Domecq *et al*., 2015), which reported that SUs and TZDs were significantly associated with weight gain.

7.5 Recommendations

7.5.1 Recommendations for healthcare professionals

7.5.1.1 Referrals to weight management programmes

As the worldwide incidence of obesity continues to increase, GPs are under increasing pressure to take a proactive lead in the prevention and treatment of the illness. Moreover, people with obesity appear increasingly willing to seek counselling for weight loss from GPs rather than from dieticians or other medical professionals (Tan *et al*., 2006). As this research highlighted a relatively low referral rate to the GCWMS, it is appropriate to make some recommendations for GPs.

In order for GPs to lead obesity management, it is necessary to increase awareness of the influence their beliefs can have on practice. GPs should be encouraged to modify these beliefs where necessary in order to facilitate this. This should be considered during the education of GPs at medical school and during their residencies, in which a lack of obesity training has to date been associated with a lower incidence of discussion of exercise and diet with patients who are obese (Rurik *et al*., 2013). Therefore, there is a requirement for improved training and knowledge in the field of obesity during GPs' education and training. Once qualified, they require access to better and more effective guidelines, wider referral options, improved tools for obesity screening and management and, importantly, greater coordination with other medical specialties. There may be some culture of discomfort surrounding the discussion of obesity. Overcoming this may be helped not only by improved training, as previously mentioned, but also by social and environmental changes. At a wider level, improved health policies, greater community involvement and a reorganization of healthcare structures and the demands placed on GPs should also be implemented.

This research demonstrates that men are less likely to participate in weight loss programmes than women, a finding consistent with previous studies. This is, perhaps, surprising, given the increasing prevalence of male obesity in the United Kingdom and the acknowledged link between obesity and poor health (Gray *et al*., 2009). However, as little research has been carried out into men's engagement and participation in weight loss programmes, this is a relatively poorly understood phenomenon. Therefore, it is important for GPs to be proactive in addressing the situation. In addition to an increased awareness of this particular aspect of the obesity problem, GPs must take responsibility for identifying

men with obesity and encourage them to enrol in weight management programmes. Initiatives that may help address the issue might include assisting with the initiation of programmes in appropriate locations, such as the workplace. Furthermore, men who are obese need to be actively motivated to reduce their weight. Increasing awareness of the health issues that may result from their high weight, particularly as they grow older, can lead to increased concern about potential serious conditions such as heart attacks, which may help encourage them to attend weight management services.

7.5.1.2 Implementing guidelines on the prescription of anti-diabetic drugs

Clinical guidelines are an important means of improving the quality of care. They are frequently developed and disseminated in healthcare systems across the world, but adherence varies greatly. There are many potential reasons for the variation in the degree to which different guidelines are followed in practice. Some examples are the means by which they are developed, the content of the recommendations, the type of problem being addressed and the body or organization disseminating the guidance (Grol and Grimshaw, 2003). Barriers to adherence to guidelines reported in a previous study included a lack of awareness of their existence, a lack of agreement with or awareness of the content, or impediments related to patients or working environments (Casey, 2013).

However, in terms of diabetes research and the resultant recommendations included in the guidelines for its treatment, changes are usually rapidly transferred to daily clinical practice. This is particularly true of drug treatments, as the major pharmaceutical companies are very proactive in promoting their products for use in hospitals, primary care settings and community pharmacies. Despite this, some GPs have continued to prescribe weight-gaining anti-diabetic medications for patients with obesity and type 2 diabetes even after the publication of the 2010 SIGN guidelines. This might be because some practitioners are not aware of the effect of these medications on weight-gain, while some of them may be aware of this effect but might be motivated by other reasons influencing their decisions, such as the cost of the drugs or GPs' habits. In addition, it might be believed that these drugs reduce the risk of complications from diabetes, based on the UKPDS study that showed that a reduction in or increased control of blood glucose (HbA1c) reduces the risk of complications. However, most studies carried out subsequent to the UKPDS have actually simply looked at reducing blood glucose without looking at the outcomes, and assumed that they would be the same. The true reasons for GPs' inertia

in terms of prescription might be determined through surveys, including those carried out online.

It might be possible to change the practice of healthcare professionals using interventions that deemed to be consistently effective. Examples might include audit and feedback, various types of reminder systems (either computerised or manual), or participation in workshops, enabling them to discuss and engage in practice in order to reach consensus that treatment guidelines for a given clinical problem are appropriate. More traditional methods, such as educational meetings on diabetes, electronic publications or audio-visual educational material, may prove less effective (Bero *et al*., 1998). A previous systematic review by Jeffery *et al*. (2015) reviewed the evidence about the effective interventions that improve adherence to the CVD guidelines. It included 38 RCTs examining different interventions, such as education, audit and feedback, academic detailing, and other interventions. The authors concluded that, despite the small number of studies and their lower quality, many interventions show the potential to improve GPs' adherence to the CVD guidelines. Educational intervention compared to usual care resulted in a statistically significant improvement in adherence to the guidelines; the mean difference was 0.58% (95% CI: 0.35 to 0.8).

In summary, GPs must review patients' anti-diabetic medication regimes prior to referral to the GCWMS. Doctors must aim to achieve familiarity with the latest guidelines on the pharmaceuticals available to them, including new drug groups and their potential effect on patients' weight.

Qualified pharmacists are increasingly involved in the prescription of medications for a limited range of indications. Broadly speaking, establishing wider, collaborative programmes for management of drug-therapy along these lines could be beneficial in the prescription of drugs to sufferers of chronic diseases or to patients with complicated drug regimes. Therefore, a further important means of improving the prescribing of anti-diabetic medication to patients with overweight or obesity would be to involve pharmacists, who could monitor the progress of patients' care between visits to their doctors. The relevant expertise of pharmacists could enable them to manage the prescription of anti-diabetic medications and monitor the patient's adherence to the prescribed regimen. For example, in the period between appointments to see their diabetes physician (which may be three or even six months), a patient could visit the pharmacist for routine monitoring. At these

visits, the pharmacist could measure the patient's BMI and blood glucose levels and use these to determine whether any changes to their lifestyle, body weight, glucose control or drugs are required in order to change their glucose control and prevent any elevation in their BMI. The process might also incorporate remote disease management technology to enable interlink patients to have more frequent monitoring while reducing the number of pharmacist visits required. If the patients could upload their blood glucose meter readings electronically each week, their BMIs could be checked when attending the pharmacist appointment and decisions regarding the onward progress of their care made at that time.

The outcomes of pharmacist interventions in the treatment of type 2 diabetes were identified by Pousinho *et al*. (2016) in a recent systematic review. The review included 36 RCTs, involving 5,761 patients in total. It found that pharmacist interventions brought about more significant improvements in multiple outcomes than was achievable with usual care; for example, in terms of HbA1c, fasting blood glucose, blood pressure, lipid profile, and medication adherence. HbA1c was evaluated in 26 studies, of which 24 yielded a greater reduction in outcome. When the intervention group was compared with the control group, the difference between the groups ranged from -0.18% to -2.1%. When measuring BMI outcomes, 14 RCTs reported mean BMI fell between the baseline and final follow-up in case where there was pharmacist intervention. The variations reported between treatment and control groups ranged from +0.4 kg/m^2 to -2.77 kg/m^2. In eight studies, a greater improvement in medication adherence was observed in the intervention groups than in the control groups, but of these, only two reported a statistically significant difference.

A further systematic review assessed the effect of pharmacists' interventions on subjects suffering from chronic kidney disease (Salgado *et al*., 2012). A total of 37 studies were identified, including 4,743 patients with kidney problems. It was found that pharmacists recognised 2,683 drug-related problems in 1,209 participants. Pharmacists' interventions reduced the incidence of end-stage renal failure in subjects with diabetic nephropathy (14.8 versus 28.2 / 100 patients), and reduced mean systolic blood pressure from 175.8 mmHg to 145.3 mmHg, p =0.02. Additionally, pharmacist interventions reduced the mean FPG in patients with chronic kidney disease from 11.6 mmol/l to 9.0 mmol/l, p =0.001.

7.5.2 Clinical implications and recommendations for the GCWMS

The findings of this research demonstrated modest results for the GCWMS compared to Weight Watchers and other commercial weight management services. Therefore, several recommendations to improve the results further are offered.

Accessibility

It is important that the GCWMS programme be as accessible as possible to everyone for whom it would be of benefit. There is wide scope for facilitating this. A wide choice of appointment times, including evenings and early mornings to enable access for people at work during the day, would encourage them to complete the programme.

Patients from the most deprived areas

Patients from areas with the highest levels of socioeconomic deprivation must be encouraged to participate in the GCWMS programme; the provision of transport would assist with this. Educational classes in more deprived areas to provide people with clear and concise information about healthcare and the benefits of weight loss and the GCWMS would increase motivation.

Physical activity

More frequent physical activity sessions might improve the engagement of young people and men, motivating them to participate in and complete the programme. It should be noted that not all interventions will suit or be effective for all people. Successful participation not only requires motivation but also requires an appropriate intervention to be selected.

Phase 2

In phase 2, the overall outcomes of the programme might be improved by increasing the frequency of the sessions (for example, holding them on a fortnightly, rather than monthly, basis) and by contacting the patients each week. Overall effectiveness might be increased by raising the intensity of the phase 2 interventions and by targeting effective interventions at more specific populations. This is based on evidence that patients lost most of their weight during the lifestyle phase of nine sessions (fortnightly), compared with phase 2.

Multidisciplinary team

Just as coordination with other specialties is a recommended course of action for GPs, it is recommended that the GCWMS should also work in conjunction with pharmacists and GPs to maximize the benefits of the service. Weight loss might be enhanced and the proportion of patients completing the programme increased by including these three groups on the management team. As well as the ability to supply medicine safely (and to identify suitable patients to whom it could be administered), pharmacists' expert knowledge regarding drugs would enable the provision of information and advice about adverse side-effects and interactions, as well as monitoring participants to maximise the drug's efficacy. The physicians' role might include working with dieticians to provide advice on healthy lifestyles, exercise and nutrition. Practice nurses may be a useful addition to the team as they can improve overall diabetes care by monitoring risk factors, ensuring attendance at screening, work with the GP to optimise medications and insure that individuals have the necessary education and skills to manage the condition.

Orlistat

Orlistat was shown in the systematic review and meta-analysis of RCTs to be of benefit for patients with type 2 diabetes, resulting in a clinically significant improvement in glycaemic control. For this purpose, it is an effective adjunct to lifestyle intervention and anti-diabetic drugs among patients who are obese and overweight with this form of diabetes. The review showed that there were statistically significant differences in absolute weight loss between treatment and control groups. As the mean difference between the groups was sometimes small, the clinical significance is uncertain, making this a decision for healthcare professionals involved in the treatment of patients with obesity. It is important to consider the possible adverse effects of orlistat when considering its use in patients' treatments.

Some differences were observed between the weight loss achieved through orlistat reported in the RCTs and its effect in the GCWMS. The GCWMS studies found weight loss to be lower than the figure derived from the systematic review and meta-analysis of the RCTs. In GCWMS, the mean weight loss at seven months was -2.93 kg (95% CI: -3.8 to -2.0 kg); from the meta-analysis, the mean weight loss at three months was -3.67 kg (95% CI: -4.30 to -3.04 kg). Differences in selection criteria, programme setting and the intensity of support may have contributed to these differences. These differences are summarized in the table below:

Differences	RCTs	GCWMS
Inclusion criteria	BMI ≥25 kg/m^2	BMI ≥30 kg/m^2
	Participants with type 2 diabetes	Participants with type 1 or type 2 diabetes
Intervention	Orlistat + lifestyle change for 3 months	Lifestyle intervention for 4 months, then orlistat for 3 months
Support	- Individual treatment	- Group support
	- Regular weight checks	- Monthly weight checks
	- Contacting patients regularly by phone	- Monthly session

Table 7-1 Differences between using orlistat in RCTs and in real life weight management service.

Using orlistat from the beginning of the lifestyle intervention might therefore improve weight loss in the GCWMS. This therefore highlights the need for a post-approval evaluation of the effectiveness of orlistat as delivered in a weight management programme centre or in routine primary care.

Target weight loss definition

The lifestyle treatment phase of GCWMS is clinically effective for patients completing the treatment programme. However, for patients with BMI ≥40 kg/m^2, other risks might not be improved by a weight loss target of ≥5 kg, and this goal may be insufficient. Therefore, the weight loss target for the GCWMS might need to be reviewed and a higher target set.

Medication prescribing

This thesis has provided evidence to support the effect of anti-diabetic drugs on weight change. The results suggest that referral to lifestyle weight management with appropriate hypoglycaemic agents is a suitable course of action be considered for all patients who are obese with type 2 diabetes. These medications should be prescribed on an individualised basis, and the regimen should take into account the patient's current BMI and weight profile.

7.5.3 Obesity prevention in Scotland

Obesity is a growing problem and forecasts predict that it will continue to affect the health and economy of the population in the future. There is a clear link between the difference in a person's intake of food and expenditure of energy and their weight change, as demonstrated through energy gap models. Excess energy intake is one of the driving factors of the increase in obesity.

Scotland provides a good quality and different range of interventions for the treatment of obesity, but very much needs to take action on obesity prevention. Governments are the most important players in terms of reducing the obesity epidemic; the promotion and protection of public goods including public health – is one of their key responsibilities (Gortmaker *et al.*, 2011). Therefore, it is critical for the government to monitor childhood and adult obesity, as well as the main aspects of the living environment that affect them and are affected by them. While the use of higher taxes might be effective at reducing obesity (for example, increasing the duty on alcohol and foods with a high caloric content to discourage consumers from purchasing them too frequently), there are arguably more positive measures that can be taken. One government department, the Food Standards Agency, is responsible for protecting public health with regard to food. It is important that they continue to work towards reducing obesity and to support the food and drink industry in this aim. The proportion of low-energy food and drinks must be increased at the expense of energy-dense alternatives, and products must continue to be altered to reduce portion sizes, salt and sugar content and saturated fat content. Clear product labelling enables consumers to choose healthier options. The government should play a role through its educational departments, working with the food industry to provide more nutritious meals to children. Schools themselves must also play their part, both through physical education and through measures such as teaching about healthy eating and reducing television viewing.

Physical activity increases energy expenditure; increasing such activity is an effective intervention in helping to prevent obesity. Therefore, it is essential that each community has access to a suitable physical environment for children to enjoy a positive healthy lifestyle. Provision of facilities in the workplace and community to enable adults to exercise (for example, swimming, walking, running, cycling or jogging) would also be of benefit. Furthermore, obesity prevention is known to be strongly associated with sustainable food supply and poverty reduction, and taking measures to achieve these

objectives is likely to result in benefits in terms of reducing obesity (The Scottish Government, 2010).

7.5.4 Future Research

This is the first research into the effect of anti-diabetic medication on weight loss in patients with diabetes who referred to weight management programmes. Indeed, research into the effectiveness of such weight management programmes themselves remains an emerging field in the United Kingdom. Therefore, it is expected that the studies presented in this thesis will provide a foundation for future research. Such research is required both to corroborate the findings of the thesis and to investigate the new questions that have arisen from the studies described in it.

Two issues that emerged were that women and young people are less likely to achieve their target weight loss, while men are less likely than women to enrol in weight management programmes. Further research is required to investigate the potential reasons for these factors. There was a noticeable difference in the weight loss determined from the meta-analysis of the RCTs and that seen at GCWMS; it is suggested that a further study should be carried out to confirm this. Furthermore, it is recommended that a direct comparison of the effect of orlistat on blood glucose control between RCTs should be made in a prospective study of real life data from the GCWMS. Further research into orlistat trials is also recommended to investigate the effect of physical activity and placebo on weight loss, HbA1c and FPG, as there is currently a lack of studies in this area. Moreover, if the GCWMS starts offering orlistat at the beginning of the lifestyle phase, further research in the form of a RCT into the use or non-use of orlistat in patients with type 2 diabetes at the start of the lifestyle interventions is recommended.

As this research evaluated the effectiveness of two phases of the weight management programme (the lifestyle phase (four months) and phase 2 (three months)), a study investigating the maintenance phase would be beneficial. When combined with this work, such a study over a 12-months period would provide a comprehensive evaluation of the effectiveness of the GCWMS. It should be standardised rolling evaluation built into GCWMS with set reports so that the effect of any changes can be monitored in a timely fashion and acted upon. In addition, qualitative research or employing a questionnaire would be useful to assess the reasons for a higher dropout rate, and might help to improve the completion rate. This thesis represents one of the first analyses of the patterns of prescribing and subsequent effects of anti-diabetic drugs on weight change in patients referred to GCWMS. Combining the findings of Chapters 5 and 6 with the dataset and patients' hospital records would provide a significant baseline dataset for a study into the

overall effectiveness of the programme. This would enable a study to be carried out to examine the effect of the doses of anti-diabetic drugs on weight loss in patients who have completed the entire programme. In addition, it would be interesting to study the association between weight loss and any changes in prescribed medications, as well as the effect of GCWMS on diabetes outcomes by conducting a cohort study. It would be valuable to conduct a piece of qualitative research, employing a survey or interviews, to consider the reasons why guidelines are not followed, since practitioners continue to prescribe weight-gaining anti-diabetic drugs for patients with obesity.

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Appendix 1: Mean weight loss by the number of session attended at the lifestyle phase

Number of session	N (7,329)	%	Mean weight change and 95% CI (kg)
2 sessions	734	10.0	-0.54 (-0.6 to -0.3)
3 sessions	664	9.1	-1.17 (-1.3 to -0.9)
4 sessions	553	7.5	-1.57 (-1.8 to -1.3)
5 sessions	540	7.4	-2.1 (-2.4 to -1.7)
6 sessions	836	11.4	-3.06 (-3.3 to -2.8)
7 sessions	1,326	18.1	-3.72 (-3.9 to -3.5)
8 sessions	1,599	21.8	-5.23 (-5.4 to -5.0)
9 sessions	1,077	14.7	-6.64 (-6.9 to -6.3)

Appendix 2: Permission to use GCWMS data

Acute Services Division

Rehabilitation and Assessment Directorate

NHS Greater Glasgow and Clyde

Glasgow & Clyde Weight Management Service

Mansionhouse Unit
100 Mansionhouse Road
Langside
GLASGOW, G41 3DX
Tel 0141 201 6115
Fax 0141 201 6117
E-mail gwms@ggc.scot.nhs.uk
Website www.nhsggc.org.uk/gcwms

Mr Nasser M N Aldekhail
Flat 4/2, Renfrew Chambers
136 Renfield Street
Glasgow
G2 3AU

Date: 20th December 2013
Your Ref:
Our Ref: SB/SA
Enquiries to: Dr Susan Boyle
Extension: 0141 201 6115

Dear Nasser

Re: Request for access to GCWMS data

Thank you for your letter requesting permission for access to data from GCWMS. Your request was discussed at GCWMS Operational Research Group meeting on 4th December 2013 and there was agreement in principle to permit access.

As a next step, we would like to invite you to our next meeting on Wednesday, 19th March 2014 at 9.30 am to allow you to present your proposal to the group. We would like to hear what your research questions are and more detail on the data/variables you wish to examine.

Please let me know if you will be available to attend the meeting on the above date.

Yours sincerely

Dr Susan Boyle
Consultant Clinical Psychologist
Glasgow & Clyde Weight Management Service

cc: Dr David Morrison, Chair of Research Group

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