

WEIGHT MANAGEMENT AND CHRONIC DISEASE

Wilma S Leslie

RGN, BA, MSc

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Glasgow Royal Infirmary,

Glasgow,

Scotland

©

Abstract

Background: Obesity, in addition to being a serious condition in its own right, is causally associated with many chronic non-communicable diseases, and its prevention, identification and treatment is a public health priority.

Results: The main findings of the present thesis were that 1) many drugs, used in the management of chronic disease, have an adverse effect on body weight with weight change of +10kg observed as a real side effect of some. 2) Identification and management of obesity is not a formal part of current practice in many secondary care clinics. While acknowledging the adverse health effects of obesity within their specialist areas, clinicians felt under-skilled and insufficiently resourced to provide effective management. 3) Improvements in iron status in pre-menopausal women can be achieved during weight loss, using eating plans that either include or exclude red meat. The data while in-conclusive suggest that a diet including red meat may confer greater benefits on iron status.

Discussion: Weight gain is an adverse effect of many drugs used to treat chronic diseases. This should be discussed with patients prior to treatment and advice provided on how to avoid or minimise weight gain. NHS secondary care consultants are concerned about obesity and its impact on their patient's health. Most have no weight management strategy and would like one. This will require additional training and resources. Excluding red meat did not adversely affect iron status in pre-menopausal women. A larger study is required for definitive health promotion advice.

Conclusion: Pharmacotherapy is a significant factor in the rising prevalence of obesity. Weight management is not an integral part of patient care in secondary care clinic settings. The exclusion of red meat during weight management does not compromise iron status in pre-menopausal women with low iron stores.

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Authors Declaration

I declare that the work contained in this thesis is original, and I am the author of this thesis. The planning and design of the studies reported within this thesis were completed by myself, in collaboration with Dr C Hankey and Professor M Lean. Recruitment of study participants and delivery of study interventions were carried out by myself, as were anthropometric measurements and venesection for haematological measures. Laboratory measurements were conducted by the Department of Pathological Biochemistry at Glasgow Royal Infirmary. Data entry and analysis were carried out by myself with guidance from Mr Harper Gilmour, Statistician, University of Glasgow Department of Public Health and Health Policy. I am the principal author of the papers which have been published.

Wilma S Leslie

Supervisors Declaration

Certify that the work reported in this thesis has been preformed by Wilma S Leslie and that during the period of study she has fulfilled the conditions of the ordinances and regulations governing the degree of Doctor of Philosophy.

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Publications arising from the present thesis

Full Papers

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Leslie WS, Hankey CR, McCombie L, Lean MEJ. (2005) Weight management: a survey of current practice in secondary care NHS settings in 2004. *Journal of Evaluation in Clinical Practice* **11**, 462-467.

Abstracts

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List of Abbreviations

Adj2	Adjacent to
BHF	British Heart Foundation
BMI	Body Mass Index
BMR	Basal Metabolic Rate
COMA	Committee on Medical Aspects of Food Policy
CVD	Cardiovascular disease
DOH	Department of Health
ED	Energy Deficit
FTO	Fat mass and obesity
HEBS	Health Education Board for Scotland
MAFF	Ministry of Agriculture and Fisheries
NAO	National Audit Office
NDNS	National Diet and Nutrition Survey
NICE	National Institute for Health and Clinical Excellence
RCT	Randomised Controlled Trial
RTM	Regression to the Mean
SEE	Standard Error of Estimates
SEHD	Scottish Executive Health Department
SHS	Scottish Health Survey
SIGN	Scottish Intercollegiate Guideline Network
SPSS	Statistical Package for Social Sciences
WHO	World Health Organisation

Summary

Chronic non-communicable diseases are now a significant cause of disability and death. Obesity, in addition to being a serious condition in its own right, is causally associated with many non-communicable diseases and its prevention and treatment is now a public health priority. As the development of obesity is a multi-factorial process, prevention and management will require multifaceted interventions which address the many contributory factors.

The aims of the present thesis were:

- 1) To determine the effect that “obesogenic” drugs have as an adverse effect on body weight.
- 2) To determine the current practices in relation to weight management currently provided for overweight/obese patients attending different secondary care outpatient clinics in Scotland.
- 3) To determine the effect of a programme for weight loss and maintenance, which included the regular consumption of red meat in comparison to one that excluded it, on iron status in young women, recruited from work-sites.

In order to achieve these aims in 3 separate studies, a range of techniques used in Human Nutrition research were employed. A postal questionnaire survey, a systematic review and randomised controlled study were carried out. This PhD training was thus able to include aspects of the aetiology of obesity and of its management with an assessment of practice in relation to current guidelines and so contribute to this evidence base.

Aetiology of obesity: obesogenic drugs

Several drugs, or categories of drugs, listed by the WHO and other writers, and used in the treatment of chronic disease, are consistently associated with weight gain as a side effect and considered “obesogenic”. However the extent to which they may contribute to the multi-factorial process behind obesity is not well documented.

An electronic search of Medline 1966-2004, Embase 1980-2004, PsycINFO 1967-2004, and the Cochrane Register of Controlled trials identified 43 randomised controlled trials that fulfilled the inclusion criteria for this systematic review. In the majority of studies the main objective was to compare the efficacy and safety of drug therapy for a separate endpoint, but with weight change recorded under safety outcomes. Weight change was a primary outcome measure in only 6 studies. There was evidence of weight gain for all the drugs included, up to 10kg at 52 weeks.

The review provides evidence of the weight gain potential of some common drugs. It is perhaps only now, in light of the present epidemic of obesity, that this undesirable effect on body weight has become a highly pertinent issue. Weight change up to a mean +10kg has been observed in good quality controlled trials as a real side effect of some drugs. Data on body weight are often not recorded in published clinical trials or is reported in insufficient detail. This side effect has potentially serious consequences, should be mentioned to patients, and weight management measures routinely considered when prescribing drugs known to promote weight gain. Future clinical trials should always document weight changes.

Attitudes, beliefs and current practice in secondary care for weight management

One hundred consultant clinicians were surveyed, using a postal questionnaire, to determine current practices with regard to the identification of and management of overweight /obesity in patients attending different secondary care outpatient clinics.

The overall response rate was 55%. However, only 9% (5) of clinicians reported having a protocol in place for the management of patients who were overweight or obese. Lack of expertise and inaccessibility to expertise were cited frequently as reasons for having no protocol in place. Fifty one percent felt that weight management (including obesity treatment) should be undertaken by a specialist service either run by general practitioners (GP), or by clinicians in a secondary care setting. Around one-third of all those surveyed reported a willingness to incorporate obesity management within their own routine specialty practice.

Clinicians acknowledged that there were adverse health effects of obesity within their specialist areas, but felt under-skilled and insufficiently resourced to provide effective management. Effective prevention and management are required to challenge the obesity epidemic and will require the involvement of both primary and secondary care NHS settings. It was encouraging that a third of respondents felt prepared to incorporate obesity and weight management within their routine specialist practice.

Replacing Myth with evidence in weight management: Avoiding Meat

Iron deficiency is major global public health problem and common in the UK especially in pre-menopausal women. Habitual dieting can deplete iron stores especially if intake of haem-iron is restricted but also iron rich bread and cereal foods are restricted. Women often specifically exclude red meat while slimming, which has potential implications for iron status. Their avoidance of meat does not emerge from evidence based advice and

seems to have arisen from myth. A randomised clinical study was designed to evaluate the effect of a weight loss diet that included the regular consumption of red meat, compared with a diet that excluded red meat. Thirty six overweight, pre-menopausal women, with a mean serum ferritin 15.8 (SD 3.1) ug/l (normal range 10.0-275.) entered the study. Dietary advice was delivered using a one-to-one approach with review every two weeks.

Thirty women completed the study. Weight change at week 12 was -2.8 (SD1.9) kg, $p < 0.0001$ (meat), -2.6 (SD 2.4) kg, $p < 0.0001$ (no meat). Serum ferritin improved in both diet groups at wk 24, with no significant difference between the groups. This increase was significant for the groups combined +3.24 (SD 9.02) ug/l ($p = 0.03$). This increase will have represented regression to the mean, as subjects were recruited on the basis of low ferritin. There was some suggestion ($p = 0.07$) that in women consuming meat, better adherence to dietary advice, with greater weight loss, led to greater improvements in serum ferritin. However observing $p < 0.05$ as the unit of significance, this study concluded that excluding red meat did not adversely affect iron status over 24 weeks, conversely, including meat did not impede weight loss. Serum ferritin improved in both diet groups and was the result of all participants consuming a diet that was rich in sources of both haem and non-haem iron. The data, although inconclusive, suggest better iron status with regular consumption of red meat. A larger study with greater weight loss is required for definitive health promotion advice to women with low ferritin. Including red meat should be an option in any weight management programme. It provides a variety of other nutrients as well as haem-iron.

Chapter 1

Introduction

1.1 Obesity and Non-communicable diseases

Diet and lifestyle are acknowledged to be important factors in the maintenance of health and the prevention of disease. Over the last few decades the lifestyle and diets of many populations has changed significantly, with diets becoming richer in high-fat, high-energy foods, while lifestyles have become more sedentary. A consequence of these changes is that chronic non-communicable diseases related to overweight and obesity including diabetes mellitus, cardiovascular disease (CVD), hypertension and stroke, and some types of cancer, are increasingly significant causes of disability and premature death (Table 1.1) the need to promote healthier diets and lifestyles to prevent chronic disease has long been advocated (WHO 2003), but obesity rates are climbing rapidly in most post-industrial countries

1.1.1 Diabetes

In addition to being a serious condition in its own right obesity, and/or the diet and lifestyles that promote it, is associated with many of the other non-communicable diseases and most spectacularly with type 2 diabetes. Increases in obesity over the past 30 years have been paralleled by a dramatic rise in the prevalence of diabetes. Over this time-frame the incidence of type 2 diabetes in the US is reported as doubling with much of the increase observed among people with a BMI ≥ 30 kg/m² (Fox *et al.*, 2003). Diabetes risk increases as soon as BMI rises above 23kg/m² and Relative Risks approach 100 with BMI >35 kg/m² (Carey *et al.*, 1997). As people become more overweight at younger ages (www.heartstats.org, SHS 2003, www.diabetes.co.uk) so type 2 diabetes and its vascular complications will emerge at younger ages and total prevalence increases. It is anticipated that type 2 diabetes will become one of the major public health issues of this century (Williams, 1999).

1.1.2 Cancer

There is less, but rapidly increasing, recognition that increased body weight can lead to the development of cancer. (McMillan *et al.*, 2007, World Cancer Research Fund, 2006). The evidence that body fatness is a cause of certain cancers is reported as convincing for cancers of: - oesophagus, pancreas, colon and rectum, postmenopausal breast cancer, endometrium and kidney. Maintaining a healthy body weight is recommended as “one of the most important ways to protect against cancer” (World Cancer Research Fund 2006). In the US it is estimated that obesity could account for 14% of cancer deaths in men and 20% in women (Calle *et al.*, 2003). UK data show that increasing BMI is significantly associated with increased risk of developing cancer and in post-menopausal women 5% of cancers can be attributed to obesity (Reeves *et al.*, 2007), - i.e. they would not have occurred without obesity. UK data for both men and women estimate that 4% of all cases of cancer could be avoided if BMI's exceeding 25kg/m^2 could be avoided (Cancer Research UK 2006). The differences between UK and US data may reflect the differing prevalence of obesity, the US having a higher rate than the UK (Centres for Disease Control and Prevention 2008, British Heart Foundation 2006). However as obesity prevalence continues to rise in the UK it is likely that the percentage of cancer cases attributable to obesity will increase also.

1.1.3 Hypertension

The association between overweight/obesity and hypertension is well recognised (Garrison *et al.*, 1987, WHO, 1998). Indeed excess weight is considered one of the strongest predictors of hypertension with the incidence more frequent in obese people in comparison to lean counterparts (Poirier *et al.*, 2006). More recent research suggests that increased visceral fat accumulation, with large waist circumference, is the best marker and predictor of hypertension rather than obesity without central fat distribution (Iacobellis & Sharma, 2006). Moderate weight loss has a beneficial effect on cardiovascular risk factors

including hypertension, with the greatest benefits seen soon after weight loss (Aucott *et al.*, 2005). There may be permanent effects of prolonged obesity on blood pressure regulators, as after weight loss hypertension recurs when weight has stabilised, even after bariatric surgery (Sjostrum *et al.*, 2000).

1.1.4 Stroke

While the relationship between obesity and CHD is well established the association between obesity and stroke is more complicated (Hu *et al.*, 2007). Some studies have shown a relationship (Folsom *et al.*, 1990, Rexrode *et al.*, 1997, Kurth *et al.*, 2002) whilst others do not (Curb & Marcus, 1991). High blood pressure is an important causal factor. As with hypertension recent research suggests that abdominal adiposity more than BMI is associated with an increased risk of stroke in men (Hu *et al.*, 2007, Suk *et al.*, 2003).

1.2 Factors influencing the development of overweight and obesity

1.2.1 Genetics

It is well documented that familial factors are important but estimates of heritability vary markedly the lowest being 5% and the highest 90% (Loos & Bouchard, 2003). So-called “simple obesity” occurs when a person’s individual makeup is susceptible to an environment that promotes excess energy consumption over energy expenditure, (Mutch & Clement, 2006). In contrast to the rare identification of single gene mutations that cause obesity, the identification of any specific polygenic profile associated with the development of “simple obesity” is proving more elusive (Fisler & Warden, 2007). It is likely to be a complex situation involving several genes that will result in individuals being predisposed to obesity but only after prolonged exposure to environmental factors (Hitman, 1998). As an example a recent candidate gene to be identified is the FTO (fat mass and obesity) gene. Those with a common variant in this gene are said to be 70% more likely to become overweight or obese in comparison to those who do not (Frayling *et al.*, 2007). It

is not explained how the variant in the FTO gene actually causes this modest increase in risk of weight gain. Many people with this gene do not become obese, so it may contribute to risk under some conditions. It is not sufficient to have the gene to become obese as its effect can be overcome. Moreover as the gene pool has remained essentially stable over several generations (Marit & Martinez, 2006), the rapid increase in obesity cannot be explained by changes in genetic makeup and it is the environment that is exerting the most powerful influence.

1.2.2 Energy Intake

Food availability and food choice determine the macronutrient composition of the consumed diet and will have a significant influence on energy intake. This, alongside physical activity, is considered one of the major influencing factors on the increasing prevalence of overweight and obesity (WHO, 2003, Keith *et al.*, 2006, Popkin, 2006). In epidemiological studies high-fat energy-dense diets are strongly associated with the increase in the prevalence of obesity (WHO, 1998). It has been observed that in countries where obesity is common the percentage of fat in the diet has been high for many years at around 40% of energy intake (WHO, 1998). However there is much debate on the strength, and on the causality of the relationship between dietary fat and the rising epidemic of obesity. Dietary fat has a much higher energy density than other macronutrients but a lower satiating effect. It is argued that the low satiety factor results in passive over-consumption and hence high fat diets contribute more to the development of obesity than low/lower fat diets (Bray & Popkin, 1998, Bray *et al.*, 2004). Other researchers suggest, on the basis of self-reported dietary data, that the percentage energy from fats has fallen (Willet & Liebel, 2002).

Since the 1960's the available dietary energy, measured in kilocalories, has risen by approximately 450 kcal/d per person (WHO, 2003). It is agreed that the overall increase in

calorie intake is a significant contributory factor in the obesity epidemic, but there is confusion over exactly what it is doing. In fact only a small excess (10-20kcal/d) is enough to cause weight gain, (i.e. fat accumulation) but most of the increased energy consumption is to support the higher BMR of a more overweight population. One element of increased energy consumption is larger portion sizes (Schwartz *et al.*, 2006). Portion sizes, offered by retailers and in catering have risen markedly since the 1980's, mirroring the rising prevalence of obesity (Young & Nestle, 2002, Schwartz *et al.*, 2006). Increases are most evident in convenience foods and foods eaten outside the home (Church, 2008). Larger portion sizes eaten out-with the home may distort an individual's perception of what is a normal portion size thus leading to larger portion sizes being served within the home (Schwartz *et al.*, 2006). The portion sizes of foods eaten at home (breakfast cereals, breads etc) chosen by a sample of young people were found to be significantly greater than those chosen by a similar population 20 years previously (Schwartz *et al.*, 2006).

Eating out-with the home has become more popular and in the US the increase in the number of per capita restaurants (fast-food and full service) is estimated to have accounted for 65% of the rise of the percentage of the population classified as obese (Chou *et al.*, 2004). . In the UK expenditure on foods eaten out-with home has increased by 29% over the last decade (Cabinet Office., 2008) accounted for ~12 % of total energy intake in 2006 (Defra, 2008). While this perhaps represents a small proportion of total energy intake it may, as suggested previously, influence portion sizes of other foods eaten in the home.

The proportion of energy from fat is higher in foods from catering sources (McCrorry *et al.*, 2000, Prentice & Jebb, 2003). The contribution of "fast foods" to the increasing prevalence of obesity was reviewed as part of the recent World Cancer Research Fund publication (WCRF 2006). Six studies showed that increased consumption of fast foods significantly increased the risk of weight gain in adults. There was also some evidence of

this effect in children. The authors concluded that “the evidence that fast foods are a cause of weight gain, overweight and obesity is strong and consistent”. This effect is likely to be due to excess energy intake (Prentice & Jebb, 2003). Also noted was that fast foods are often available in large portion sizes.

1.2.3 Energy Expenditure/Physical activity

For most individuals in society today there is a reduced requirement for physical activity in both working and domestic life (WHO 2003, Di Pietro *et al.*, 2004). In the UK we now travel 25% less by foot and by bicycle, have more labour saving devices, fewer people are involved in physically demanding jobs, we watch more TV and have less participation in sport (Foresight, 2007). The relationship between physical activity and weight gain is unclear. In many studies an inverse relationship between physical activity is seen, in others the results are inconsistent (Foglehom *et al.*, 2000). One review concluded that there was uncertainty as to whether physical activity can prevent weight gain (Wareham *et al.*, 2004). More recent data from the National Weight Control Registry suggest that high physical activity is vital to avoid weight regain (Cattenaci *et al.*, 2008). Tsofliou *et al.* have suggested that, on the basis of earlier work by Mayer, there may be a threshold level of physical activity, above which weight gain does not occur. Below this level appetite is de-regulated (Tsofliou *et al.*, 2003). However while the evidence base requires strengthening current guidelines for physical activity should be adhered to.

Current guidelines for physical activity advocate 30 minutes on most days of the week, a level that is sufficient to reduce the risk of many chronic diseases (Blair & LaMonte, 2005). In Scotland although the proportion of men and women meeting these recommendation has increased since 1998, nationally representative survey figures show that around 60% of both men and women still do not reach these levels (SHS, 2003). While sufficient to prevent chronic disease, this level of activity is, for many, unlikely to

be sufficient to prevent weight gain, and around 45-60 minutes per day is recommended to prevent the shift from normal weight to obesity (Saris *et al.*, 2003). Recent research also suggests that physical activity for around 275 minute per week (40 mins/day), alongside continued energy reduction, is required to sustain a 10% weight loss (Jakicic *et al.*, 2008)

It has been suggested that fitness can compensate for the effects of obesity on cardiovascular risk (Katzmarzyk *et al.*, 2004, Church *et al.*, 2004). Other studies report that even with high levels of physical activity obesity was still associated with increased total mortality (Stevens *et al.*, 2004, Meyer *et al.*, 2002). More recent research (Akbartabartoori *et al.*, 2008) suggested that these conflicting results may be due to differing populations and methodologies and aimed to clarify the picture using nationally representative cross sectional data. The authors conclude that both physical activity and weight loss are important to reduce cardiovascular risk in those who are obese, but the results confirmed that high levels of reported physical activity in obese subjects, was not enough to outweigh the effects of obesity on cardiovascular risk.

1.2.4 Other Factors – Pharmaceutical Iatrogenesis

Whilst changes in diet and physical activity are the key factors in terms of underpinning the obesity epidemic other factors have been proposed as additional influencing factors, which modify the likelihood of, or extent of weight gain (Keith *et al.*, 2006, Bray *et al.* 2005). In principle this could be through influences on 1) food choice and intakes or 2) absorption/malabsorption or 3) physical activity or 4) any of the biochemical pathways which contribute to energy expenditure (Kopleman, 2006). Currently there are many prescription drugs in use that are associated with weight gain and this contributes to “pharmaceutical iatrogenesis” (Keith *et al.*, 2006, Kopleman, 2006). Many of these are used in the treatment of chronic non-communicable diseases.

One group of drugs with a long association with weight gain is antipsychotics and several reviews have examined their effect on body weight (Cheskin *et al.*, 1999, Allison *et al.*, 2002, Abramoff Ness & Apovian, 2005). Allison *et al.*, 2001 reports that many individuals prescribed atypical antipsychotic drugs can gain more than 7% of their body weight. Prescription medications used in the treatment of non-communicable diseases such as diabetes, heart disease and hypertension are also associated with weight gain (Leslie *et al.*, 2007).

Although weight loss is common in some diseases and regain is a feature of effective treatment, for many weight gain as a result of drugs is an unwanted side effect. It contributes importantly to non-compliance and relapse of the disease being treated. Weight gain was shown to be the key mediator of non-compliance in patients prescribed antipsychotic medication. Those who were obese were twice as likely to omit their medication (Weiden *et al.*, 2004). Weight gain is also reported as factor in non-compliance with drug therapy in individuals with type 2 diabetes (Rubin, 2005).

Recent research has shown that those who are overweight or obese are more likely than those of “normal” weight to be prescribed drugs associated with weight gain (Counterweight, 2005). Comparison of 1150 obese patients with 1150 age and sex matched controls of normal weight showed a higher percentage of the obese were prescribed drugs used to treat chronic non-communicable diseases, including those considered obesogenic. This has the potential to trap individuals in a vicious cycle as any existing weight problem may be exacerbated by drug therapy.

The use of many of the drugs associated with weight gain has increased significantly over the past 30 years (Keith *et al.*, 2006). However the evidence about the amount to which they can contribute to weight gain is not widely promoted. Many previous reviews of

obesogenic drugs have been carried out, however many focus only on one class of drugs (i.e. beta-blockers Sharma *et al.*, 2001, and antipsychotics Allison *et al.* 2000), were not carried out following a systematic approach (Abramof Ness & Appovian, 2005) or do not quantify the effect on body weight (Cheskin *et al.*, 1999).

1.3 Dietary approaches for weight management

Obesity develops over time, often decades, therefore the disease process of obesity is the process of excess fat accumulation. Thus the “cure” for obesity, and primary target of weight management, is to achieve a stable weight i.e. to block the process of excess fat accumulation. For most overweight people weight loss is also desirable, but this may distract from the need to achieve weight stability and the methods may not be the same. The principles and targets of modern weight management can be traced to the SIGN Obesity report (1996):-

- 1) Prevent unwanted weight gain
- 2) Achieve weight loss (at least 5-10%)
- 3) Prevent weight gain
- 4) Improve health and risk factors of obese people, whether or not they lose weight and prevent further weight gain

There is no one method of weight loss that will suit all (Lean, 1998). Weight loss can be achieved via a wide range of approaches (Klem *et al.*, 1997), and a huge literature of lay books exists (Which, 2001). However many promote variable and often ill-advised methods including those that involve eliminating or severely restricting the consumption of particular groups of food. One of the most popular approaches over the last decade has been the Atkins Diet, which advocates limiting consumption of carbohydrates to less than 20g/d while allowing unlimited consumption of fats and protein. In comparison with other weight loss approaches, a high protein approach is probably comparable in terms of weight

loss (Dansinger *et al.*, 2005). However, attrition at one year in the Atkins group was the second highest of the four approaches examined at 48%. This suggests that the Atkins approach is more difficult to sustain over the longer term. Another research study reports no difference in weight loss between the Atkins approach and other methods at one year but also reports that adherence was poor (Foster *et al.*, 2003). So although having some success for weight loss there would appear to be no great advantage over other methods which allow consumption of all food groups.

Limiting specific food groups may have unwanted nutritional effects. Reducing fat intake, in particular saturated fats, has value for both health and weight control. However advice promoted by health professionals to reduce fat intake is interpreted by some as a need to reduce or eliminate red meat from their diets (Houston *et al.*, 1997). In a previous study (Leslie *et al.*, 2002), the effect on serum lipids of the inclusion or exclusion of red meat as part of a weight reduction diet was investigated. Anecdotal reports from participants recruited to this study suggested that excluding red meat was often a first step during slimming. One survey found that avoidance of red meat was one of the most highly adopted behaviours for reducing fat intake. Red meat was replaced by fish and poultry only some of the time by the majority of survey participants. Reduced consumption of foods more likely to affect fat intake were ignored. Such dietary behaviour also has implications for iron intake (Capps *et al.*, 2002).

Today it is non-haem iron, found in cereal products, which provides most of dietary iron (Gregory *et al.*, 1990). Diets low in carbohydrates may therefore also lead to a lack of iron as many of these cereal foods are fortified with iron. This problem would be aggravated by a low intake of Vitamin C, which is also common in both slimming diets and the general population of Scotland. Vitamin C is a known enhancer of iron absorption. Data

from the Women's Cohort Study has shown dietary Vitamin C intake to be positively associated with serum ferritin (Cade et al 2005).

Iron status is described as “a continuum from iron deficiency with anaemia to iron deficiency with no anaemia, to normal iron status” (WHO, 2001). Depletion of iron stores is the first stage in the development of iron deficiency and ultimately anaemia. At an early stage the mobilisation of iron from the storage compartment is initiated, serum ferritin levels fall but haemoglobin levels remain normal (Fig 1.2). While iron depletion itself has no adverse health consequences it represents an increased risk of developing iron deficiency, particularly if there is blood loss (Cook *et al.*, 1992, Watts et al 1988). Iron depletion is a common finding- in menstruating women (Duport *et al.*, 2003).

Clinical guidelines for the management of obesity in Scotland published in 1996 (SIGN) recommended a 12-week weight loss period using a 600 kcal daily energy deficit (ED) to achieve moderate weight loss. At that time this recommendation was supported only by one small non-randomised audit (Frost *et al.*, 1991). A subsequent RCT that compared the ED approach with a standard 1500 kcal approach found that compliance with advice was better with the individualised approach (ED) (Leslie *et al.*, 2002), confirming the findings of the limited research already completed in this area. Good compliance with macronutrient prescriptions to reduce fat and especially saturated fat, optimises weight loss but may also be more likely to lead to long term changes in dietary habits thus improving the likelihood of maintaining weight loss and improving long term health. The 600 kcal individualised ED (Lean & James, 1986) approach advocates a balanced diet based on healthy eating advice with no food group restricted or eliminated, and is recommended in the recently published NICE guidelines (NICE 2006).

Amongst women with poor iron status habitual dieting for weight loss is reported to have a negative effect on iron stores (Houston *et al.*, 1997). In the late 1990's approximately 38% of women in the USA reported trying to lose weight (Kruger, 2004). In the UK in 2000-2001 around 24% of women reported trying to lose weight (NDNS, vol 5 2004). Thus between one-third and one half of overweight and obese women are actively "slimming" by restricting some components of their diets. Previous research has shown that many women who attempt weight loss do not consult health professionals but follow a diet devised independently (Wardle & Johnstone 2002). As the prevalence of obesity continues to rise, as it has in both countries, so too will the number of people attempting weight loss, especially women, who are twice as likely to attempt weight loss than men (NDNS vol 5 2004).

In the United Kingdom 11% of women were found to have a serum ferritin below 15ug/l, and 8% women had a haemoglobin level below 12 g/dl (NDNS 2004,vol 4). In Scotland the prevalence of iron deficiency anaemia, defined by a haemoglobin level <12g/dl, in women aged 16-24 was reported at 7.3%, rising to 12.3% in the 35-44 age group (SHS 2003).

No effect on iron status was observed in the study carried out by Leslie *et al* (2002). However this study was carried out in a male population who do not show the same variations in iron status as pre-menopausal women. The main cause of iron depletion in men would largely be due to chronic blood loss, this is in contrast to pre-menopausal women who are susceptible to iron deficiency anaemia due to the demands of menstruation and pregnancy on their smaller iron stores. These study results therefore have little application to females. The elimination of red meat as part of slimming plans without concomitant dietary improvements may well deplete iron stores and contribute to iron deficiency and anaemia in pre-menopausal women.

Given the epidemic of overweight and obesity and the prevalence of iron deficiency, research is required to determine the best approach for weight loss, which will preserve iron status in pre-menopausal women.

1.4. Identification of overweight/obesity

The identification of those who are overweight or obese is a crucial first step in its management. Given the large numbers of overweight and obese subjects, primary care is usually identified as the most appropriate setting for weight management both in the UK and the US (SIGN 1996, Sciamanna *et al.*, 2000). There is widespread popular awareness of increasing obesity, but little incentive for routine measurement. A recent UK audit found that obesity was under-recognised in the primary care setting. Amongst 40 GP practices that had expressed an interest in weight management only two-thirds of patients had a weight or BMI recorded in their medical records (Counterweight, 2004).

The recently published NICE guideline for weight management proposes that all sectors of the NHS should be involved in the identification and management of overweight and obesity. (NICE, 2006). Many of the non-communicable diseases associated with obesity are primarily managed in secondary care settings. However, as in primary care, it has been reported that only a small percentage (<10%) of those who were overweight/obese were identified as such in secondary care clinics in the UK (Cleator *et al.*, 2002). A prospective study was then carried out to determine the actual prevalence of obesity amongst those attending secondary care clinics. Between 20-30% of those attending the clinics were identified as overweight or obese, a figure reported as below the true prevalence at that time. This situation is not unique to the UK health service as in other European countries a similar picture is also evident with obesity being recorded in only a minority of health care records. (Hauner *et al.*, 1996).

Lack of awareness amongst physicians regarding the impact of obesity on disease progression and severity it is suggested, may account for the low rate of obesity identification in clinics. It is also suggested that physicians may feel they do not have the skills or resources to deal with obesity management and this is a disincentive to identify and treat those who are overweight/obese (Cleator *et al.*, 2002).

The identification or recognition of overweight and obesity is a crucial first step in its subsequent management. Recent research has shown that an increasing number of individuals fail to recognise that they themselves are overweight or obese (Johnson *et al.*, 2008). This may, in part, be due to the normalisation of overweight in today's society (Johnson *et al.*, 2008, Foresight, 2007). However the consequence of this is that if individuals do not recognise, or choose not to recognise, that they are overweight it is unlikely they will seek help to lose weight. Even when individuals do recognise they are overweight not all attempt to lose weight (Wardle & Johnson, 2002). Conversely people who are advised to lose weight by a health professional are more likely to do so (Galuska *et al.*, 1999). It is therefore of paramount importance that health professionals raise the issue whenever possible and measure height and weight both to allow accurate determination of body mass index and to identify weight gainers. Suggested opportunities for this within the health service are "registration with a general practice, consultation for related conditions (such as type 2 diabetes and cardiovascular disease) and other routine health checks" (NICE, 2006).

Previous research has indicated that secondary care clinics, responsible for managing many non-communicable diseases to which obesity is a contributory factor, are an ideal opportunity to identify overweight/obesity and initiate treatment (Cleator *et al.*, 2002).

Clinical guidelines, which are systematically developed, are intended to aid and inform the decision making process regarding appropriate health care for specific conditions (West & Newton, 1997). Guidelines are now available for a wide range of conditions including many of those associated with obesity. Clinical guidelines for colorectal cancer, cardiac rehabilitation, prevention of cardiovascular disease, stable angina (www.sign.ac.uk), type 2 diabetes, myocardial infarction, hypertension, (www.nice.org.uk) all state the need for weight management, and that those who are overweight or obese should be advised to lose weight. However only two, (stable angina, prevention of CVD), state specifically that BMI or waist circumference should be evaluated as part of the clinical assessment. It is important that the measurements required to calculate BMI are taken as if they are not it is less likely that overweight/obese patients will be identified. The perceptions of health professionals regarding their patients' weight status is at odds with actual measurements. Research has shown that in 25% of cases physicians failed to recognise that their patients were overweight, particularly overweight men. Male physicians were less likely than females to recognise that patients were overweight (Caccamese *et al.*, 2002).

Given the associations between obesity and a wide range of non-communicable diseases further investigation of current practice with regard to weight management within secondary care clinics is warranted as all opportunities should be used to identify and initiate management of those who are overweight or obese (NICE 2006, WHO 2004).

The value of work-site settings for health promotion has been recognised (Henrikas *et al.*, 1996, HEBS, 1996, NICE, 2006). Work-sites have been described as “being to adults what schools are to children” as a significant amount of time is spent there (Goetzel *et al.*, 2008). Work-site based interventions have the advantage of reaching large numbers of people at little or no cost who may not seek help in other settings (Henrikus *et al.*, 1996, Glasgow *et al.*, 1993, Goetzel, 2008). Previous research has shown that while significant number of

workers expressed an interest in smoking cessation and weight loss, when the interventions were offered out-with the work-place uptake was only 1% compared to 8-12% when offered on site (Erfurt et al., 1990). In Scotland employers are able to access a range of initiatives aimed at improving the health of their workforce. One initiative is Scotland's Health at Work (SHAW, now known as Healthy Working Lives) which was established in 1998 and aims to "encourage and support workplaces to make the active promotion of good health an integral part of Scottish corporate culture" (Scottish Executive 2005). The workplace setting is one of the 4 major themes of the recent Scottish Executive Health Department report *Improving Health in Scotland: The Challenge*. Health promotion or occupational health personnel are in a position to target obesity and weight management and implement strategies to contribute to reducing the prevalence of obesity and associated disorders.

1.5 Research Methods Needed for Weight Management

The management of obesity incorporates prevention as well as treatment and requires multifaceted interventions to address the many aspects that contribute to its increasing prevalence. Evidence is needed from research that covers a wide range of methodologies (Lean *et al.*, 2008). This thesis includes a small selection of different research methods applicable to obesity research including aspects of research into both aetiology and management.

Aetiology

Obesity, a serious condition in its own right, is associated with many non-communicable diseases, which are now a major cause of death and disability. Many drugs used to treat chronic non-communicable diseases are associated with weight gain and considered obesogenic. Pharmaceutical iatrogenesis has been highlighted as a contributory factor in

the aetiology of obesity (Keith *et al.*, 2006, Kopleman, 2006), however it remains unclear to what extent these drugs contribute to weight gain and the development of obesity.

Management

Many of the non-communicable diseases associated with obesity, and for which drugs considered obesogenic are prescribed, are managed within secondary care settings. Consultations for obesity related conditions are a suggested opportunity to identify and initiate management of obesity (NICE 2006). Previous research in this area found little in the way of identification or management of obesity (Cleator *et al.*, 2002) and it remains unclear if or how obesity is being managed in secondary care settings. Given the present epidemic of obesity further research is required to ascertain current practice with regard to obesity management in this setting.

Many dietary approaches exist for those who are identified as overweight or obese and who wish to lose weight. However any dietary approach for weight loss should not be detrimental to health, give rise to, or exacerbate nutritional deficiencies. Iron deficiency is one of the most common nutritional deficiencies in the UK among premenopausal women (Cabinet Office., 2008). As women are more likely than men to attempt weight loss perhaps repeatedly (NDNS vol 5 2004), research to determine the best approach for weight loss while maintaining iron status is important.

1.6 Aims of thesis

1) To determine the effect that “obesogenic” drugs have as an adverse effect on body weight.

2) To determine the current practices in relation to weight management currently provided for overweight/obese patients attending different secondary care outpatient clinics in Scotland.

3) To determine the effect on iron status in young women, recruited from work-sites, of a programme for weight loss and maintenance, which included the regular consumption of red meat in comparison to one that excluded it.

These objectives are not closely related, but offered a portfolio of research methodologies appropriate to research training in obesity and weight management.

1.6.1 Research questions

RQ1 Is weight gain an adverse effect of some commonly prescribed drugs?

RQ2 Is the effect on body weight reported and quantified in studies examining these drugs?

RQ3 Are formal protocols to routinely identify and manage overweight/obese patients in place in secondary care clinics?

RQ4 Is height and weight routinely measured in secondary care clinics?

RQ5 What steps are taken to manage patients who are identified as overweight or obese?

RQ6 Does a weight reduction diet, that regularly includes lean red meat, maintain iron status in pre-menopausal women?

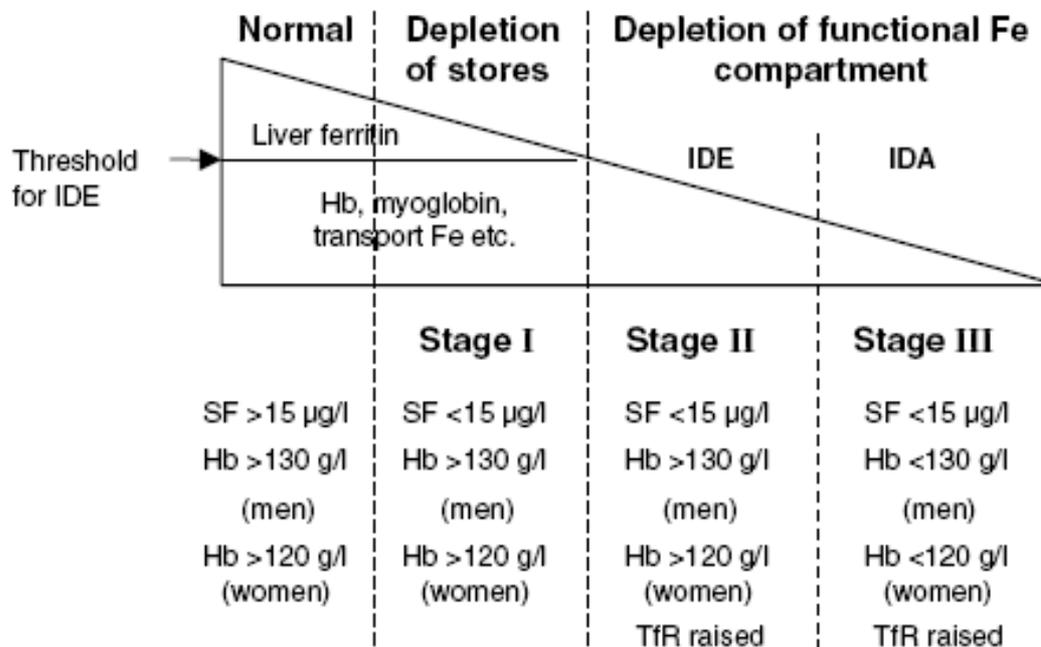
RQ7 Does a weight reduction diet, which excludes lean red meat, maintain iron status in pre-menopausal women?

RQ8 Do the effects on iron status differ between treatments?

Table 1.1 Medical Consequences of Obesity (Lean et al 2002)

Tiredness/Depression	Diabetes	Cancers
Stroke	Non-alcoholic fatty liver disease	Osteoarthritis
Idiopathic Intracranial Hypertension	Dyslipidaemia	Phlebitis
Cataracts	Gall bladder disease	Skin disorders
Pulmonary Disease	Hypertension	Gout
Coronary Heart Disease	Back pain	
Pancreatitis	Gynaecological abnormalities	

Figure 1.2 Stages in the development of iron deficiency. IDE, iron-deficient erythropoiesis; IDA, iron-deficient anaemia; SF, serum ferritin; TfR, transferrin receptor. (Fairweather Tait 2004 Adapted from Suominen et al. 1998.)



Chapter 2

Methods

2.1 Study 1: Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review

2.1.1 Systematic Reviews

The number of scientific papers published annually is extensive (Mulrow 1994) and for most researchers or health professionals review of all published papers on any given topic would be time consuming and unfeasible. A systematic literature review brings together large amounts of information and provides information about the effectiveness of interventions by identifying, appraising and summarising large quantities of research.

Well defined inclusion criteria and critical appraisal of studies allows unsound studies to be excluded and thus a systematic review presents only studies carried out using robust and reproducible methods (Greenhalgh, 1997). Systematic reviews are replicable, scientific and transparent and by following explicit methods, minimise bias. Detailed guidelines on how to conduct a systematic review are available <http://www.york.ac.uk/inst/crd/index.htm>.

The most obvious and accessible sources of data for a systematic review are electronic databases such as Medline. However even the most rigorous database search may miss relevant papers. Thus other sources should also be used and these include: reference lists of published papers, “grey literature”, unpublished sources, and raw data from published trials (Greenhalgh, 1997, NHS Centre for Reviews and Dissemination 2001).

2.1.2 Selection of Studies

For the present study an electronic search of Medline 1966-2004, Embase 1980-2004, PsycINFO 1967-2004, and the Cochrane Register of Controlled trials was performed. The drug name or drug category was the primary key word for each search i.e.:-

Antidepressive agents, Tricyclic/ae [Adverse effect]

(weight adj2 gain).mp [mp= title,abstract,cas registry/ec number word, mesh subject heading]

Combine 1 AND 2

Limit to (human and English language and all adult <19 plus years and clinical trial, randomised controlled trial, controlled clinical trial

Reference lists of all relevant papers were checked. Hand-searching of journals or searches of grey literature were not undertaken as part of this review due to time and resource constraints.

Articles were selected on the basis of title and abstract. Studies were included according to the following eligibility criteria: only randomised controlled studies were included, adult participants (>18 yrs) prescribed a drug considered obesogenic, duration of at least 3 months and compared the “obesogenic” drug with placebo, an alternative drug or other treatment. Outcome measures had to include measured weight change, which was reported quantitatively. Studies that primarily investigated the use/effect of a combination of “obesogenic” drugs were excluded, as were studies in which body weight was self-reported. For each drug those used to treat diseases characterised by weight loss (e.g. Type 1 diabetes) were also excluded.

Reference Manager Version 11 (The Thomson Corporation) was used to sort and manage all data.

2.1.3 Quality Assessment

Two reviewers checked independently that the studies identified by the search strategy met the inclusion criteria and assessed the methodological quality of the included studies. Quality assessment focussed on the adequacy of the randomisation procedure and followed

the guidelines outlined in the University of York's guide to undertaking systematic reviews (NHS Centre for Reviews and Dissemination 2001).

As the identified studies involved different populations, drugs and dosages no quantitative meta-analyses were performed.

2.2 Study 2: Weight management: a survey of current practice in secondary NHS settings in 2004

2.2.1 Postal Questionnaires

This was a postal questionnaire survey. The questionnaire used (Appendix 1) was developed by the author and peer reviewed by both supervisors. Prior to the main survey the questionnaire was piloted, by post, with a convenience sample of 9 clinicians from various clinical specialties, mainly to determine acceptability and clarity. Three clinicians included in the pilot had an interest in obesity management

Postal questionnaires are widely used in health research. Advantages include low cost and ability to collect data from a wide area. However, a major limitation is commonly a large proportion of non-responses. Previous research has recommended various strategies to maximise response rates. These include: keeping questionnaires short, use of first class post, provision of a stamped addressed reply envelope, providing non-respondents with a second copy of the questionnaire. Questionnaires on topics likely to be of interest and those originating from university also increased response rates (Edwards *et al.*, 2002). All these strategies were employed in this study.

Validity and reliability are important factors in questionnaire surveys and where possible it is preferable to use a previously validated questionnaire. It was not possible to find such a

questionnaire for use in the present survey. One aspect of validity is concerned with whether a questionnaire will collect the information that is required accurately – that is will it do what it is meant to do (face validity). Piloting gives some indication of face validity but does not ensure it. Content validity is concerned with the extent that the questionnaire covers all aspects of the topic under investigation. Literature review and inclusion of the views of experts in the area to be investigated should give a good view of the issues to be addressed (Earl-Slater 2002). A test of a questionnaire's reliability is that it yields consistent results over time. The questionnaire survey was not the sole focus of the present thesis and therefore detailed techniques to ensure validity and reliability were not pursued. It is also noted that responses to questionnaires that investigate the management of a particular condition may differ considerably from practice (Adams *et al.*, 1999).

2.2.2 Participants

Three health boards adjacent to, but out-with, Greater Glasgow were chosen. At the time of this study there was a great deal of activity within the Greater Glasgow Health Board area with regards to obesity management. A specialist obesity service was about to be piloted and a weight management programme was being trialled in primary care. It was felt that this could influence responses with regard to current practice and hence alternative health board areas were chosen. The hospitals chosen within each health board area were District General hospitals serving fairly large populations of between 78,000-230,000 people (www.scotland.gov.uk).

2.2.3 Statistical Analysis

Data management and analysis was carried out using SPSS for Windows (Version 11.5). Analysis was mainly descriptive.

2.3 Study 3: Influence of red meat consumption on iron status in dieting pre-menopausal women.

2.3.1 Study Design

The study followed a randomised controlled design. Volunteers attended for baseline assessment of height and weight to determine BMI, and for blood sampling to determine iron status. Those with a BMI greater than 25 kg/m² and a serum ferritin between 10 and 15ug/l inclusive, were randomised to either include or exclude red meat as part of their weight management programme. A blinded envelope system was used for treatment allocation. Randomisation was stratified by BMI category, (25.1-29.9, 30-34.9 and > 35 kg/m²). The randomisation sequence was produced by the study statistician, (HG), and the envelopes prepared by the principal investigator (CH) neither of whom played any part in recruitment, treatment allocation or delivery of the intervention.

2.3.2 Subjects/Recruitment

Subjects were recruited from several worksites located in West Central Scotland between April 2005 and June 2006. Recruitment was carried out using poster advertisement (Appendix 2), posted in staff areas such as canteens and female changing rooms. The posters outlined the study and gave details of when the study researcher would visit the work-site for recruitment. All subjects gave informed consent before entry into the study. Ethical Approval was obtained from the West Ethics Committee (Appendix 3).

2.3.3 Exclusion Criteria

Body mass index below 25 kg/m², those who had chosen to exclude meat permanently from their diet, post-menopausal, pregnant or less than 6 months post partum, any chronic inflammatory disease, iron replete subjects, insulin treated diabetics, any other condition

requiring prescribed food products or specialist dietary intervention, haemoglobin level <10 g/dl, serum ferritin < 10 ug/l or >15ug/l.

The normal range for serum ferritin is 10 to 275ug/l. The effects of diet on serum ferritin were considered more likely in women with serum ferritin levels at the lower end of the normal range (Dr C Tait, Consultant Haematologist, personal communication). Power calculations for the present study used data from a previous published study (Patterson *et al.*, 2001) this study also used 15ug/l as the upper limit for inclusion. The exclusion criteria of ferritin <10ug/l was imposed by the Ethics Committee.

2.3.4 Anthropometric Measurements

Height

Height was measured to the nearest mm, with the Frankfort plane horizontal, using a portable stadiometer (Chasmors Ltd, London). Body weight was measured using calibrated scales (SECA, Germany) to the nearest 100g in light clothing without shoes. All equipment was new and had been calibrated by the manufacturer.

Waist Circumference

Waist circumference was measured midway between the lowest rib margin and the lateral iliac crest, using a flexible steel tape and ensuring the skin was not compressed. (Holtain Ltd, Crymch, UK). This measurement was made twice and the mean used for analysis.

2.3.5 Assessment of Iron Status

The assessment of iron status can be made using a range of measurements that include haemoglobin (Hb), serum iron, ferritin, transferrin and transferrin receptor. Serum ferritin concentration is the most applicable, least invasive indicator of iron stores (Baynes, 1988, Goddart *et al.*, 2005). It “provides a precise quantitative measure of total iron in the

storage compartment” (Cooke *et al.*, 1992) and is recommended for the diagnosis of iron deficiency (Ross, 2002). It is also considered the “best indicator of a response to an intervention” (WHO, 2004). However serum apoferritin is an acute phase reactant protein and should be used in the absence of infection or inflammation. Serum ferritin levels less than 15 ug/l are indicative of depleted iron stores in both men and women (WHO, 2001). This level of serum ferritin has been reported as 75% sensitive and 98% specific for iron deficiency (Ross, 2002).

2.3.6 Haematological Measurements

Venesection was performed to collect samples for full blood count analysis. Participant’s reticulocyte count was also examined at baseline to exclude excessive blood loss as a cause for any potential iron deficiency. All samples were analysed by the Dept of Pathological Biochemistry at Glasgow Royal Infirmary using standard protocols.

Ferritin was measured on an Abbot Architect i2000. Reticulocyte count and haemoglobin were measured on a Sysmex XE 2100. Tests were analysed on an ad hoc basis and not in batches. At the time of the study (2005-2006) the inter assay coefficient of variance for ferritin was ~7.2%, ~1.2% for haemoglobin and ~21% for reticulocyte count (David Cameron, Haematology Laboratory Manager, Glasgow Royal Infirmary, personal communication).

2.3.7 Prediction Equations for Basal Metabolic Rate

The equations most commonly used in healthy subjects in the UK are the Schofield equations (Schofield *et al.*, 1985). Twelve equations by gender and age have been developed to allow the calculation of basal metabolic rate (BMR) from weight for infants, children and adults. While providing a quick and accessible method of determining energy requirements the limitations of the equations must be acknowledged. The original data on which they were based are said to include a disproportionate number of Italian subjects and

their universal applicability has been questioned. Their accuracy in those with a BMI >30 kg/m² has also been questioned (Horgan & Stubbs, 2003). However in a clinical situation they are the quickest and least invasive method of calculation energy requirements. New equations have been developed but an expert consultation concluded that they were not robust enough to be adopted and that the Schofield equations and their Standard Error of Estimates (SEE) should continue to be used. (WHO, 2001)

The equations for estimating BMR from body weight used in the dietary study were:

Women	18-30 years = 0.0621 x actual weight in kg + 2.0357	SEE 0.497
	31-60 years = 0.0342 x actual weight in kg + 3.5377	SEE 0.465

2.3.8 Diet Intervention

The approach to be used for the weight management advice was derived from the SIGN guidelines for obesity management (SIGN, 1996), with individualised advice aimed at achieving a daily energy deficit of 600 kcal (Lean & James, 1986). This approach has been widely used in clinical trials for weight management, and has proved more effective than a fixed diet prescription of 1200 or 1500 kcal/day (Leslie *et al.*, 2002, Frost *et al.*, 1991). It is also recommended in the recent NICE guidelines for weight management (NICE, 2006).

For the initial 12-week weight loss period subjects' received individualised energy prescriptions. These were calculated using Schofield equations (Schofield *et al.*, 1985). An additional activity factor, 1.3 x BMR, was then applied to calculate the energy required to remain weight stable. As the aim was to induce weight loss, a fixed energy deficit was introduced by subtracting 600-kcal from the individual's estimated daily energy requirements.

Macronutrient composition of the two eating plans in both groups was designed to provide greater than 50% energy from carbohydrate, less than 35% energy from total fat and under 20% from protein (COMA, 1991). Advice was also given to all subjects to restrict or avoid alcohol consumption. The intervention was delivered by the study researcher (WL) who was not blinded to treatment allocation.

Maintenance Period

The two eating plans (meat vs. no meat) were continued during the 12-week structured weight maintenance period. However dietary advice during the weight maintenance period followed a non-prescriptive approach. Healthy eating advice, as described by the balance of good health, was reviewed with all participants. Participants were advised that there could be some increase in the portion size of the components of main meals. The composition of main meal was directed by the plate model, a tool to assist dietary education (Armstrong & Lean, 1993). Two versions exist, a 2-component model, for meals with rice or pasta meals, and a 3-component model for meals comprising meat/fish, vegetables and potatoes. Both versions ensure that meals provide >50% dietary energy from carbohydrate and <35% energy from fat (MAFF, 1993) (Appendix 4). All participants continued to attend for review every 2 weeks throughout the maintenance period.

2.3.9 Detailed Dietary Advice

An eating plan employing standardised principles has been devised within the Department of Human Nutrition and used in previous weight management studies (Hankey *et al.*, 1997). In order to encourage the consumption of a varied diet the plan is based on an exchange system for three groups of food “bread”, “meat” and “fruit”. The “bread” exchanges comprise foods rich in complex carbohydrates such as bread, cereals, rice, pasta

and potatoes. The “fruit” exchanges are rich in carbohydrate and will provide the main source of simple sugars, although some jam or marmalade is permitted in order to ensure the palatability of bread (Appendix 5). All participants were encouraged to increase their consumption towards the dietary compositional targets (COMA, 1991).

The University of Glasgow eating plan allows the daily consumption of red meat. Participants’ randomised to include red meat were advised to consume this at least five times per week in the form of quality lean cuts. Prior to the commencement of this study the eating plan was revised to provide a plan that excluded red meat. Fish, poultry, eggs and cheese were included in the “meat” exchange category of the eating plan (Appendix 5). Portion sizes for an exchange of each food type from each of the three food exchange groups are described in household measures. The sizes were calculated using the guide to average portions (MAFF, 1993). If advice to consume a variety of red meat was followed, the available dietary iron would range from 0.4mg to 3.6mg per 100g of which 50-80% would be haem iron (FSA, 2002). Consumption of a variety of poultry and fish would give a range of dietary iron of 0.4 to 5.1 mg per 100g with a haem iron content of 20-40% (Lombardi *et al.*, 2002, Rangan *et al.*, 1997, Gomez-Basauri *et al.*, 1992).

Individual energy prescriptions ranging from a minimum of 1200 to a maximum 2600 kcal daily have been calculated in increments of 100 kcal per day using various combinations of these exchanges. For each of the exchange groups mean energy provision and macronutrient composition were calculated. The calculations were completed with the assumption that subjects would choose to eat a variety of foods from the different exchange groups, and as such their intake should be as close as possible to the relevant dietary targets.

2.3.10 Dietary Intake Assessment

There are many methods available to assess dietary intake and all have limitations (Bingham 1987). Prospective methods such as weighed intakes are expensive and time consuming for participants and require a certain degree of literacy. The main disadvantage of retrospective methods, which includes food frequency questionnaires, is that they rely on memory and there may also be a tendency give desirable answers which may lead to over and under reporting of some food items. All methods are subject to errors and biases from misreporting. Obese subjects consistently provide artificially low, incomplete inventories of their food intakes (Heitmann & Lissner 1995, Lara *et al.*, 2004).

The choice of method depends on the need and the research question. Immediate short-term intake can be estimated from prospective methods (diaries, photographic weighed or household measures) or using 24-hour recall. Longer term food exposures are most commonly estimated from forms of dietary history or food frequency questionnaires. For the present study in overweight/obese subjects it was recognised that quantitative estimates and specifically energy intakes would be unreliable because of misreporting. For the purposes of this study it would have been difficult on practical grounds to carry out a prospective dietary analysis such as weighed intakes. Previous research using weighed intakes had a high attrition rate (Leslie *et al.*, 2004) and this was amongst people who in the main were not in employment. As the present study population were mostly in full time employment the practicalities of weighing food at work, it was felt, was likely to increase the likelihood of attrition and increase misreporting.

The aims of the dietary intake assessment in the present study were to determine if advice to improve intake towards UK dietary recommendations had been implemented, the relevant part of the diet being in the past. Therefore dietary practices were assessed using

the Dietary Targets Monitor (Lean *et al.*, 2003), (Appendix 6). This short food frequency questionnaire, developed for use in the Scottish Health Survey has been evaluated against a longer food frequency questionnaire (Bolton & Milne., 1991). The evaluation was carried out in 1085 adults aged 25-64yrs from the Glasgow MONICA study population. The study showed that the Dietary Targets Monitor had the capacity to monitor dietary change toward the adult food targets of fruit and vegetables starchy foods and fish (Lean *et al.*, 2003). The advantages of using this method were ease and uniformity of administration, low cost and less burdensome for participants

2.3.11 Study Power and Numbers

The principal outcome measure was change in serum ferritin at 24 weeks post-commencement of intervention. Secondary outcome measures included changes in serum ferritin at 12 weeks, body weight at 12 and 24 weeks and meat, fruit and vegetable consumption.

Power calculations for serum ferritin were based on parameters derived from a published study of iron deficient women of child-bearing age (Patterson *et al.*, 2001). The calculated sample sizes were increased to compensate for an anticipated dropout rate of 30%. A study based on **25** analysable patients per group (it was planned to recruit **33** per group allowing for 30% dropouts) would have power of 80% to detect as statistically significant a difference between the baseline to week 24 changes in the two study groups of 6.8 units in serum ferritin and would represent a clinically meaningful improvement.

2.3.12 Statistical Analysis

Data were managed and analysed using the software package SPSS (Version 14).

Analysis of the primary outcome measure (serum ferritin) was based on analysis of covariance techniques (ANCOVA) using a generalised linear model (GLM) framework as the groups were unbalanced at baseline. The mean differences (Standard Error (S.E), 95% confidence intervals and corresponding p-values are reported.

Comparisons of weight change between the diet groups were made at 12 and 24 weeks using two sample t-tests and corresponding 95% confidence intervals. Paired t-test analysis was used to examine within group differences at 12 and 24 weeks.

The non-parametric Sign test was used to test whether a significant number of subjects in each group increased or decreased favourably their eating habits. The effect of the diet programmes and meat advice were examined by estimated odds ratio.

All analyses of iron status and weight were carried out on an “intention to treat” basis. Intention to treat analysis used the last recorded measurement, where available, for those who dropped out. If the only recorded measurement was that at baseline zero change was assumed.

Chapter 3

Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review

This chapter represents a body of work from which a paper has been published. Leslie et al, *Quarterly Journal of Medicine*, 2007; **100**:395-404. (Appendix 8)

3.1 Introduction

Obesity continues to increase in prevalence (DOH 1995, SIGN 1996, WHO 1998). In the UK around half of women and two thirds of men are overweight or obese (SHS 1998, NAO, 2001). Recent Scottish data show that the figure for women has risen to 60% (SHS, 2003). In addition to being a major health problem in its own right, obesity is associated with a range of serious symptoms and co-morbid conditions. The estimated cost to the UK Health Service of obesity and related conditions at present is immense (NAO 2001, Walker, 2003). If the rise in obesity continues it is thought that by the year 2010 one third of all adults in the UK will be obese (Williams, 1999), and the costs to health care services will have risen to an estimated £3.6 billion (NAO 2001).

Obesity is a consequence of energy imbalance, when energy intake exceeds energy expenditure over a prolonged period of time. Social and environmental forces have a powerful influence over energy intake and expenditure and individuals vary in their susceptibility to these influences due to genetic and biological factors. It is the interaction of all these elements that gives rise to obesity (WHO, 1998). Currently there are many prescription drugs in use that are associated with weight. For some, e.g. certain serotonin reuptake inhibitors and oral contraceptives, the evidence to support an effect on body weight is considered less consistent (Keith *et al.*, 2006), while others are consistently associated with weight gain and are considered obesogenic (WHO, 1998, Lean 1998, Pijl & Meinders, 1996, Finer 1998) (Table 3.1). This effect can arise as a consequence of differing mechanisms such as increased appetite (corticosteroids) or reduced metabolic rate (beta-adrenoceptor blockers) (Pijl & Meinders, 1996). For some drugs weight loss may have occurred as a result of the underlying disease and recovery on effective treatment will

include weight regain, which would not be considered an adverse effect. However in many cases weight gain is an unwanted side effect. These drugs are used in the management of chronic disease and therefore prescribed on a long-term basis. Previous research has shown that 9% of adults attributed weight gain to drugs they were prescribed (Vossenaar *et al.*, 2004).

The development of obesity is a long-term multifactorial process to which these obesogenic drugs play a contributory role. The aim of this review was to quantify the effect that the drugs, listed in Table 1, consistently reported as obesogenic, and used in the treatment of chronic disease, may have as an adverse effect on body weight. The hypothesis to be tested in this study was weight gain is an adverse effect of some commonly prescribed drugs.

The study was devised to address the following research questions:

RQ1 Is weight gain an adverse effect of some commonly prescribed drugs?

RQ2 Is the effect on body weight reported and quantified in studies examining these drugs?

3.2 Results

A total of 628 titles and abstracts were reviewed and 139 publications were retrieved and reviewed in greater detail. From these 43 studies, involving a total of 25,663 subjects, were identified that met our inclusion criteria. The main reasons for exclusion were: study duration less than 12 weeks, non- randomised study design, weight gain not reported or not quantified (Fig 3.1).

3.2.1 Valproate

All four studies compared valproate with an alternative drug, no placebo controlled studies were identified. Comparison was made with olanzapine in the treatment of bipolar disorder (Zajecka *et al.*, 2002) and acute mania (Tohen *et al.*, 2003). The objective of both these studies was to compare the drugs in terms of efficacy and safety. Biton *et al.*, (2001) compared valproate with lamotrigine in patients with epilepsy. The aim of the fourth study (Privitera *et al.*, 2003) was to determine the efficacy and safety of topiramate in comparison with carbamazepine and valproate monotherapy in the initial treatment of newly diagnosed epilepsy.

Weight change was the primary outcome measure in only one study (Biton *et al.*, 2001), and a secondary measure to assess safety in the remaining studies. The mean dosage of valproate differed in each study (Table 3.2).

3.2.2 Lithium

Only one study fulfilled the inclusion criteria and compared lithium with carbamazepine as a prophylactic agent in bipolar disorder (Coxhead *et al.*, 1992). The main outcome measure was relapse with weight gain recorded as an assessment of side effects. The initial dose of lithium was 400mg twice daily.

3.2.3 Atypical Antipsychotics

In three studies olanzapine was compared with placebo in the treatment of alcohol dependence disorder (Guardia *et al.*, 2004) and borderline personality disorder (Bogenschutz & Nurnberg 2004, Zanerinin & Frankenburg 2001). Ziprasidone was compared with placebo in the treatment of schizophrenia (Arato *et al.*, 2002). In the remaining studies comparison was made between an atypical antipsychotic and an alternative drug: clozapine, olanzapine, and risperidone with haloperidol (Czobor *et al.*,

2002), olanzapine with sodium valproate (Zajecka *et al.*, 2002, Tohen *et al.*, 2003), olanzapine with haloperidol (Tran *et al.*, 1999, Lieberman *et al.*, 2003), risperidone with amisulpride (Sechter *et al.*, 2002), clozapine with chlorpromazine (Lieberman *et al.*, 2003), olanzapine vs. aripiprazole (McQuade *et al.*, 2004) and olanzapine vs. amisulpride (Mortimer *et al.*, 2004).

Only two studies (Czobor *et al.*, 2002, McQuade *et al.*, 2004), specifically examined weight change as a primary outcome, in the remainder of the studies clinical response was the primary outcome with weight change recorded as a means of assessing safety.

3.2.4 Corticosteroids

Only one randomised controlled trial was identified (Prummel *et al.*, 1993) and compared prednisone with radiotherapy in the treatment of Graves' ophthalmopathy.

Comparison of the efficacy and tolerability of the treatments was the objective of the study, clinical response being the primary outcome measure. Weight change was recorded as a side effect.

3.2.5 Insulin

The studies included were restricted to the treatment of Type 2 diabetes. In all studies insulin therapy alone was compared with either oral agents (Nathan *et al.*, 1998, Tovi *et al.*, 1996, UKPDS 1998) or with insulin plus oral agents (Chow *et al.*, 1995, Yki-Jarvinen *et al.*, 1992, Yki-Jarvinen 1997). The dosage of insulin varied in each study and was calculated according to participant's body weight and subsequently adjusted dependent on blood glucose results.

3.2.6 Sulphonylureas

In two studies treatment with a sulphonylurea was compared with placebo only (Simonson *et al.*, 1997, Bautista *et al.*, 2003), with another oral hypoglycaemic agent and placebo in two studies (Segal *et al.*, 1997, Johnstone *et al.*, 1998), with insulin in two studies (Nathan *et al.*, 1998, UKPDS 1998), and an alternative oral hypoglycaemic agent in three studies (Campbell *et al.*, 1994, Marbury *et al.*, 1999, Tan *et al.*, 2004). Weight change was examined as a primary outcome measure in only one study (Campbell *et al.*, 1994). In the UKPDS study the main objective was to determine the risk of micro or macro-vascular complications with weight change recorded under adverse events. The objective of the remaining studies was to determine efficacy, safety and tolerability, with clinical response as the primary outcome measure and weight change recorded under safety outcomes.

3.2.7 Thiazolidinediones

Three studies compared a thiazolidinedione with placebo in type 2 diabetic patients. Patel *et al.*, (1999) assessed the metabolic effects of 4 doses of rosiglitazone, Iwamoto *et al.* (1996) investigated the efficacy and safety of troglitazone and Wallace *et al.*, (2004) examined the effect of pioglitazone on beta cell function and insulin sensitivity. The metabolic effects of pioglitazone were compared with metformin in one study (Scherthaner *et al.*, 2004), in the final study pioglitazone was compared with glimepiride with regard to changes in glycaemic control and insulin sensitivity (Tan *et al.*, 2004). In all studies weight change was measured as a secondary outcome.

3.2.8 Tricyclic Antidepressants

All three studies compared the efficacy and tolerability of a tricyclic antidepressant with an alternative anti-depressant. Paroxetine in comparison with nortriptyline (Weber *et al.*, 2000), bupropion compared with doxepin (Feighner *et al.*, 1986) and mirtazapine with

amitryptiline and placebo (Montgomery *et al.*, 1998). Weight change was the primary outcome measure in one study (Weber *et al.*, 2000), and assessed as an adverse event in the other two. The dosage of tricyclic antidepressant was not reported in one study (Weber *et al.*, 2000) and differed in the other two.

3.2.9 Beta- Adrenergic blocking agents

Two studies compared the effect on lipid profiles between a chosen beta-blocker and an alternative anti-hypertensive agent: captopril vs. metoprolol (Foss & Jensen, 1990) and nifedipine vs. atenolol (Houston *et al.*, 1991). The effect of long-term treatment with propranolol on body weight study was the main outcome in one study (Rossner *et al.*, 1990). Two studies compared treatment with a beta/blocker with bendroflumethiazide, one investigated the metabolic effects (Berglund *et al.*, 1986), the other compared the effects on mortality (Wikstrand *et al.*, 1988). Wilhelmsen *et al.*, (1987) compared beta-blocker treatment with diuretic treatment to determine difference in the incidence of non-fatal myocardial infarction, coronary heart disease mortality and total mortality.

3.2 10 Cyproheptadine

No studies were identified that fulfilled the inclusion criteria.

3.2.11 Methodological quality of included studies

All studies included in this review were described as randomised however in the majority of papers (72%) the methods of randomisation and concealment were not described. In one study (Chow *et al.*, 1995) the method of randomisation (consecutive and alternate) was inadequate (CRD Guidelines 2001). In 11 studies the method of randomisation was clearly described and considered adequate. Inclusion and exclusion criteria were clearly described in all studies. Intention to treat analysis was carried out in 51% of studies.

3.2.12 Weight Change

In the majority of studies weight change was not a primary outcome measure but was measured and recorded under safety outcomes. Weight change was a primary outcome measure in only 6 studies (Biton *et al.*, 2001, Czobor *et al.*, 2002, McQuade *et al.*, 2004, Campbell *et al.*, 1994, Weber *et al.*, 2000, Rossner *et al.*, 1990). The effects on body weight differed greatly amongst the different categories of drugs. In the majority of studies weight gain was the result of treatment with some of the greatest weight gains seen in subjects prescribed anti-psychotic medications. However in some studies weight loss was observed (Table 3.2).

Six studies investigated whether weight gain was dose related. Results varied with three studies reporting no relationship between drug dosage and weight gain (Biton *et al.*, 2001, Arato *et al.*, 2002, Czobor *et al.*, 2002). Some correlation was observed between dosage of insulin and weight gain (Chow *et al.*, 1995, Yki-Jarvinen, 1992). One study (Patel *et al.*, 1999) suggested that a clinically significant increase in body weight might be observed at higher doses of rosiglitazone.

3.3 Study Limitations

The drugs included in the present review were those consistently reported in medical/scientific literature, used in the treatment of chronic disease and believed to affect weight (WHO 1998, Keith *et al.*, 2006, Lean, 1998, Pijl & Meinders, 1996, Finer, 1998). We acknowledge that many other drugs prescribed today may also affect weight. Few studies included in the review examined weight change as a primary outcome and in many instances the variability of weight change was not reported. Studies that primarily investigated the effect of a combination of “obesogenic” drugs were excluded, however it was not always possible to be certain that other drugs known to favour weight gain were

not also being taken. However the process of randomisation should have ensured that any such confounding effect would have been similar in all groups.

3.4 Discussion

Weight change occurs over time and against a background of progressive weight gain in the “normal” population. There is no ideal time to examine the possible obesogenic effects of drugs. It can be assumed that most such drugs will have a most marked effect early in treatment, reaching a plateau effect by 6-12 months (although all healthy subjects are likely to continue to gain weight at around 1kg per year) (Hietman & Garby, 1999, Phelan *et al.*, 2003).

If the underlying disease for which the drug was prescribed has caused weight loss then recovery on effective treatment will include weight regain. The primary treatment of Type 1 diabetes is an obvious example. This was not considered an obesogenic effect and such studies were excluded by our own inclusion criteria.

The effect of the drug treatment on body weight was reported in all of the studies in this review and provides evidence that weight gain is associated with some drugs and is a major and continual burden on public health. All of the drugs included in this review are used in the treatment of chronic disease. In the UK it is estimated that around 2.5 million people have been diagnosed with coronary heart disease (BHF 2008) and beta-blockers, unless contraindicated, have a prominent role in its management (NICE 2000, SIGN 2001, SIGN 2001). Valproate is one of the first line treatments for epilepsy (SIGN 2003) and also used in the treatment of manic episodes associated with bipolar disorder. In Scotland around 20,000 – 40,000 people have active epilepsy with about 2-3,000 new cases per year

(SIGN 2003). In England 380,000 people suffer from the disease (one in 130 people) (DOH 2003). Bipolar disorder is the third most common mood disorder after major depression and schizophrenia, and affects around 1% of the population (NICE 2002). Around 1.3 million people in the United Kingdom suffer from either Type 1 or Type 2 diabetes (BHF 200). In the light of these figures the number of individuals in the population receiving treatment with an obesogenic drug is potentially quite high. In Scotland alone the number of prescriptions dispensed for beta-blockers and tricyclic antidepressants between 2004 and 2005 exceeded one and two million respectively (Table 3.3), (Audrey Thompson, Medicines Management Advisor, NHS GG&C, personal communication).

It is generally accepted that during adult life most people will gain weight. The rate at which weight is gained varies but a 0.5-1kg gain per year is considered average in the general population (Heitmann & Garby, 1999, Phelan *et al.*, 2003). In some studies in the present review weight gain in excess of this was observed over a much shorter duration, in particular those involving anti-psychotic drugs. Olanzapine and clozapine were associated with the greatest weight gains, a finding that concurs with previous reviews in this area (Allison *et al.*, 1999, Ness-Abramof *et al.*, 2005). The weight gains with beta-blocker therapy were relatively small but more marked in those prescribed propranolol. Previous research has identified propranolol as the beta blocker most likely to cause weight gain (Cheskin *et al.*, 1999, Sharma *et al.*, 2001).

In the UK at present a significant proportion of the population are considered either overweight or obese (NAO 2001, SHS 2003). It is therefore likely that prior to treatment with a drug known to favour weight gain many individuals will already be overweight and struggling to avoid further gain. The additional effect of obesogenic drug therapy may tip the balance to increase BMI towards the obese category or be sufficient to make co-

morbidities clinically apparent. Given the common and long-term use of many of these drugs it is likely that they play a significant contributory role in the increasing prevalence of obesity.

Non-compliance with any drug therapy is a widespread problem (Wertheimer & Santella, 2003) and around half of patients prescribed long-term medication for the management of chronic diseases do not comply fully with treatment (Perkins, 2002). Poor compliance with drug therapy may lead to a worsening of the underlying condition and contribute to increased health care costs (Osterberg & Blasche, 2005). Non-compliance is reported as an issue with many of the drugs included in this review (Osterberg & Blasche, 2005, Hertz *et al.*, 2005, Lowry *et al.*, 2005, Weiden *et al.*, 2004) and the weight gain associated with them may contribute to this. For those prescribed anti-psychotic medication weight gain is acknowledged as a major cause of non-compliance (Weiden *et al.*, 2004). It is unclear whether this known side effect is routinely discussed with patients prior to prescription but this should be done on medico-legal grounds. The treatment of anti-psychotic induced weight gain is now considered a treatment priority and research on approaches to address this is a growing area (Werneke *et al.*, 2003, Ohlson *et al.*, 2004, Ball *et al.*, 2001, Vreeland *et al.*, 2003, Littrell *et al.*, 2003). It would seem greatly preferable to discuss the probability of weight gain as a side effect and to provide effective advice and support to avoid weight gain. For a number of the drugs classes included weight management should form an essential part of treatment for the underlying disease e.g. Type 2 diabetes, hypertension and access to dietitians should be routine. For other drugs – notably anti-psychotics - provision of dietary advice is a new consideration (Lean & Pajonk, 2003).

This review provides evidence of the weight gain potential of some common drugs. It is perhaps only now, in light of the present epidemic of obesity, that the negative effect on body weight is a more pertinent issue. Body weight and height are routinely recorded in

virtually all clinical trials, but seldom reported. The potential of weight gain should be discussed with patients prior to the institution of therapy both for medico-legal grounds and to ensure that weight maintenance is promoted and adhered to.

Healthy eating advice, appropriate for all sectors of the population (www.food.gov.uk), should be advocated to those prescribed obesogenic drugs and may help minimise weight gain in the first instance. For those who experience weight gain the 600 kcal individualised ED (Lean & James, 1986) approach, discussed previously, which advocates a balanced diet based on healthy eating advice, is an appropriate approach for weight loss. It is recommended in the recently published NICE guidelines (NICE 2006) and its effects on nutritional status are investigated in a later chapter of this thesis (Chapter 5).

3.5 Conclusion

This study has provided answers to the following research questions:

RQ1 Is weight gain an adverse effect of some commonly prescribed drugs?

RQ2 Is the effect on body weight reported and quantified in studies examining these drugs?

It has shown that a range of commonly prescribed drugs do cause weight gain (RQ 1). The effect is relatively modest for most drugs but few pharmaceutical trials have reported data on weight change adequately (RQ2). It is a most unwelcome side effect and liable to be suppressed in publications. Patients often attribute weight gain and obesity to prescription drugs (Vossenaar *et al.*, 2004). They are often correct. Some individuals gain much more than the mean and an underlying weight problem may exacerbate the problem. These drugs almost certainly impede weight management although specific evidence is lacking. If these drugs are prescribed then patients need to be warned about side effects, and advised on how to avoid weight gain. Again no specific research had evaluated

preventative interventions, but the approaches examined in the remainder of this thesis would be appropriate.

Table 3.1 Drugs known to favour weight gain

Drug	Main use
Insulin, sulphonylureas, thiazolidiniones	Diabetes
Beta blockers	Hypertension
Corticosteroids	Inflammatory disease
Cyproheptadine	Allergy, hay fever
Antipsychotics	Psychosis
Sodium Valproate	Epilepsy
Tricyclic antidepressants	Depression
Lithium	Bipolar disorder

WHO, 1998; Keith *et al.*, 2006; Lean, 1998; Pijl & Meinders, 1996; Finer, 1998

Figure 3.1 Flowchart of progress of papers through the review.

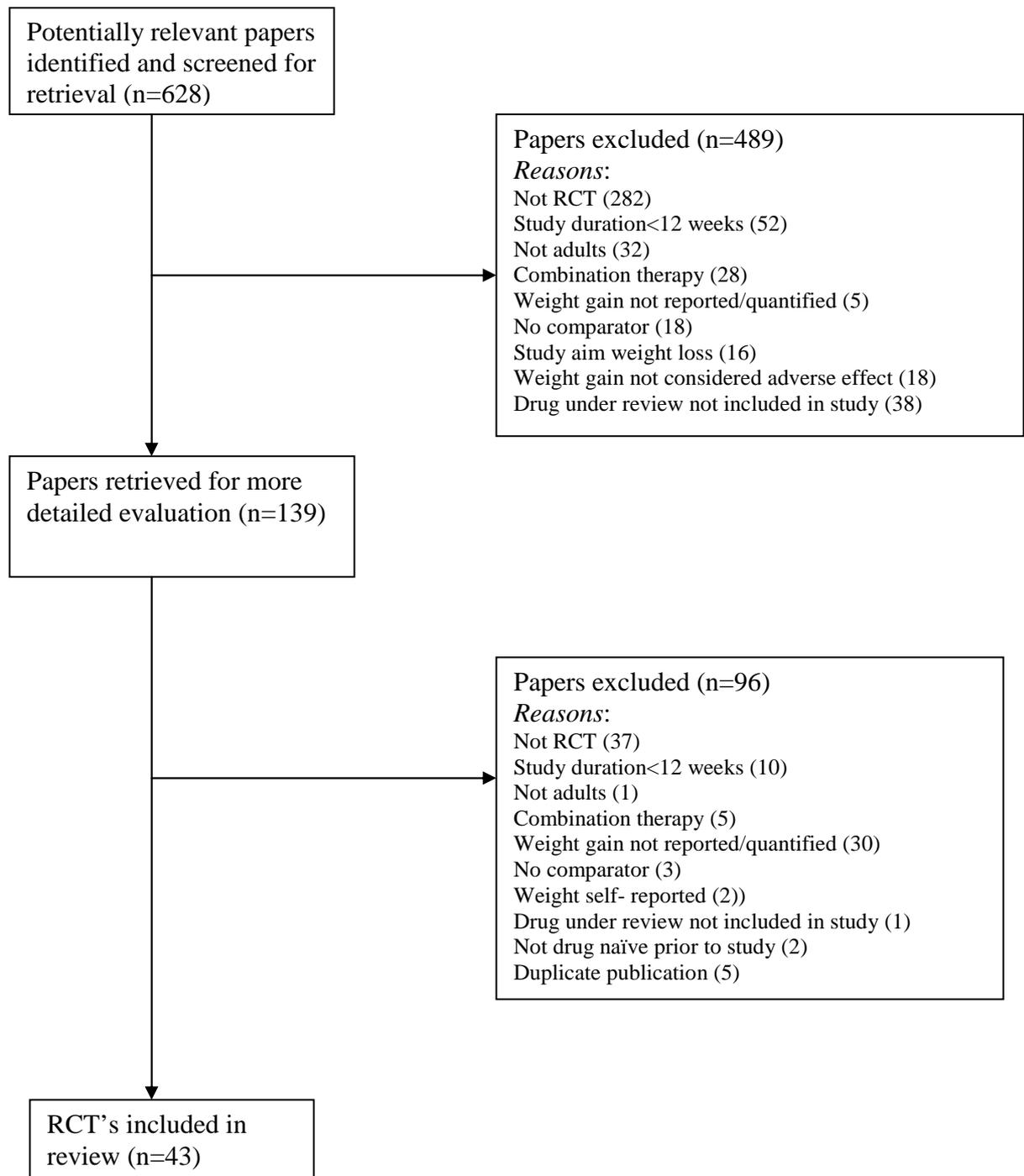


Table 3.2 Drugs and their effect on body weight

Drug	Reference	Condition	Follow up (wks)	n	Dose	Weight change (kg)
Valproate	Zajecka 2002 [#]	Bipolar disorder	12	120	2115mg/d*	+2.5**
	Biton 2001	Epilepsy	32	141	1822mg/d*	+5.8 (SD 4.2)
	Tohen 2003	Bipolar disorder	47	251	1500mg/d*	+1.2(SE 1.2)
	Privitera 2004	Epilepsy	26	621	1250mg/d	+2.0**
Lithium	Coxhead 1992	Bipolar Disorder	52	32	≥400mg/d	+4.0**
Clozapine	Czobor 2002	Schizo-affective disorder	14	151	200-800mg/d	+4.2 (SD 4.7)
	Lieberman 2003	Schizophrenia	52	160	≤400 mg/d	+9.9**
Olanzapine	Zajecka 2002 [#]	Bipolar disorder	12	120	14.7mg/d*	+3.9**
	Lieberman 2003	Psychosis	12	263	9.1mg/d*	+7.1 (SD 6.1)
	Czobor 2002 [#]	Schizo-affective disorder	14	151	30.4mg/d*	+5.4 (SD 4.6)
	Zanerini 2001	Borderline personality disorder	24	28	5.3mg/d*	+2.8 (SD 5.7)

Drug	Reference	Condition	Follow up (wks)	n	Dose	Weight change (kg)
	Tohen 2003 [#]	Acute Mania	47	251	16.2mg/d*	+2.8**
	Tran 1999	Schizo-affective disorder	51	110	11.5mg/d*	+5.0 (SD 7.3)
Olanzapine	Guardia 2004	Alcohol dependence	12	60	5-15mg/d	+4.3**
	Bogenshutz 2004	Borderline personality disorder	12	40	2.5-20mg/d	+3.7 (SD 3.4)
	McQuade 2004	Schizophrenia	26	317	10-20mg/d	+4.2**
	Mortimer 2004	Schizophrenia	26	377	5-20mg/d	+3.9 (SD 5.3)
Risperidone	Czobor 2002 [#]	Schizo-affective disorder	14	151	7.9mg/d*	+2.3 (SD 2.8)
	Sechter 2002	Schizophrenia	24	309	4-10mg/d	+2.1**
Ziprasidone	Arato 2002	Schizophrenia	52	294	40mg/d	-2.7**
					80mg/d	-3.2**
					160mg/d	-2.9**
Prednisone	Prummel 1993	Graves Ophthalmopathy	24	56	Decreasing 60-2.5mg/d	+2.0**

Drug	Reference	Condition	Follow up (wks)	n	Dose	Weight change (kg)
Insulin	Yki-Jarvinen 1992	Type 2 Diabetes	12	153	2 injection	+1.8 (SD 0.5)
					multiple injection	+2.9 (SD 0.5)
					2 injection	+5.2(SD 4.1)
	Nathan 1988 [#]	Type 2 Diabetes	36	31	1 injection	+6.6**
	Tovi 1996	Type 2 Diabetes	52	35	2 injection	+3.9**
	Yki-Jarvinen 1997	Type 2 Diabetes	52	100	2-4 injection	+5.1 (non-obese) (SD 0.6) +4.5 (obese)(SD 1.1)
Glipizide	UKPDS 1998 [#]	Type 2 Diabetes	10yrs	3867	1-2 injection	~+6.5**
	Simonson 1997	Type 2 Diabetes	16	143	5-60mg/d	-0.3 (SD 0.2)
				204	5-20mg/d	-0.1 (SD 0.1)
	Campbell 1994	Type 2 Diabetes	52	48	5-30mg/d	+2.6**
	Marbury 1999	Type 2 Diabetes	52	576	0.5-12mg/d	+3.6**

Drug	Reference	Condition	Follow up (wks)	n	Dose	Weight change (kg)
	Johnstone 1998	Type 2 Diabetes	52	411	1.25-20mg/d	+2.3**
	Nathan 1988 [#]	Type 2 Diabetes	36	31	2.5-10mg/d	+3.8**
Glimepiride	Bautista 2003	Type 2 Diabetes	14	70	1-4mg/d	+2.3**
	Tan 2004 [#]	Type 2 Diabetes	52	244	2-8mg/d	+0.8**
Glibenclamide	UKPDS 1998 [#]	Type 2 Diabetes	10 yrs	3867	2.5-20mg/d	~+4.0**
	Segal 1997	Type 2 Diabetes	24	201	3.5mg/qid	+1.4**
Chlorpropamide	UKPDS 1998 [#]	Type 2 Diabetes	10yrs	3867	100-500mg/d	~+5.0**
Troglitazone	Iwamoto 1996	Type 2 Diabetes	12	284	400mg/d	+0.06(sd 1.6)
Rosiglitazone	Patel 1999	Type 2 diabetes	12	380	0.05mg/d	-0.95**
					0.25mg/d	-0.54**
					1.0mg/d	+0.18**
					2.0mg/d	+0.36**
Pioglitazone	Wallace 2004	Type 2 diabetes	12	30	45mg/d	+0.70(SE 0.6)
	Tan 2004 [#]	Type 2 diabetes	52	244	15-45mg/d	+1.5**
	Schernthaner 2004	Type 2 diabetes	52	1199	≤45mg/tid	+1.9**

Drug	Reference	Condition	Follow up (wks)	n	Dose	Weight change (kg)
Nortriptyline	Weber 2000	Depression	12	32	n/a	+3.7(SD 2.3)
Doxepin	Feighner 1986	Depression	13	147	100-225mg/d	+2.7**
Amitriptyline	Montgomery 1998 ⁽⁵¹⁾	Depression	104	217	max 280mg/d	+1.7(SD 4.1)
Atenolol	Houston 1991	Hypertension	13	49	56mg/d*	+1.0**
Atenolol or metoprolol	Wilhelmson 1987 ⁽⁵⁷⁾	Hypertension	45mnths	6569	100/200mg/d	+1.1**
Metoprolol	Wikstrand 1988	Hypertension	208	3234	174mg/d*	+1.5**
	Foss 1990	Hypertension	26	114	50-200mg/d	+0.5(females)** +0.7(males)**
Propranolol	Rossner 1990	Post myocardial infarction	52	3837	Not stated	+2.3**
	Berglund 1986	Hypertension	10yrs	106	80mg/bd*	-0.6**

* mean dose

** SD or SE not reported

denotes duplicate reporting of studies as a result of the comparator in each study

Table 3.3 Prescribing by GP practices in Scotland April 2004- March 2005

Drug Class	No of prescriptions
Beta blockers (BNF 2.4)	2,936,456
Atypical antipsychotics	275,114
Lithium	81,252
Sodium Valproate	193,064
Tricyclic antidepressant	1,134,611
Intermediate and long acting insulins	352,632
Short acting insulins	105,207
Suphonylureas	442,833
Pioglitizone	36,898
Rosiglitizone	65,458
Glucocorticoid therapy (BNF 6.3.2)	517,366

Chapter 4

Weight management: a survey of current practice in secondary NHS settings in 2004

This chapter represents a body of work from which a paper has been published. Leslie *et al*, *Journal of Evaluation in Clinical Practice*, 2005; **11**:462-467. (Appendix 9)

4.1 Introduction

The estimated cost to the health service of obesity and related conditions, compared to people with ideal or normal weight, is immense (NAO 2001) and the development of strategies for the prevention and treatment of obesity and overweight is now a priority for health promotion and education (DOH 1992., WHO 1998,). Given the large numbers of overweight and obese subjects (43% and 22% of the entire adult UK population), and its wide variety of clinical manifestations, it is recommended that weight management should usually be undertaken in primary health care, community or commercial sectors (SIGN 1996). Attempts are being made to establish a structured approach to weight management in the primary care setting as a recent audit has shown that both the identification of obesity and overweight and its subsequent management are at present sub-optimal (Counterweight Project Team 2004a).

In addition to being a major health problem in its own right, obesity contributes to a range of co-morbid conditions, importantly including type 2 diabetes mellitus, hypertension, hyperlipidaemia, coronary heart disease, stroke, several major cancers, back-pain, arthritis and depression (WHO 1998). Many of those diagnosed with co-morbid conditions such as diabetes, hypertension, coronary heart disease and depression are likely to be prescribed drugs known to favour weight gain (Leslie *et al* 2007).

The management of most of these conditions is conventionally co-ordinated from a secondary care specialist setting. This setting provides an opportunity to identify and initiate management of an underlying weight problem if it is contributing to pathology.

However it is unclear if, or how, the management of obesity is currently addressed in this setting and what links exist with primary care to ensure comprehensive and effective management.

The aim of this study was to determine the current practices in relation to weight management currently provided for overweight/obese patients attending different secondary care outpatient clinics. The study was devised to address the following research questions:

RQ3 Are formal protocols to routinely identify and manage overweight/obese patients in place in secondary care clinics?

RQ4 Is height and weight routinely measured in secondary care clinics?

RQ5 What steps are taken to manage patients who are identified as overweight or obese?

4.2 Participants and Methods

The study was carried out in 3 NHS Trust areas in Scotland, between January and March 2004. Ethical approval was sought from each trust however formal ethical approval was, in each case, deemed unnecessary, as neither the process nor the questionnaire raised ethical issues.

Questionnaires were sent to 100 consultant clinicians working in a range of specialist areas (endocrinology, orthopaedics, obstetrics and gynaecology, cardiology, general medicine, respiratory medicine, rheumatology, general surgery) in five District General Hospitals within the three trust areas. These hospitals were chosen to represent a range of rural/urban and socio-economic environments. One reminder letter, including a repeat questionnaire, was sent to non-responders after 2 weeks.

The postal, self-completed questionnaire, which had been piloted with 9 clinicians, comprised 8 questions to determine:

- a) if a formal protocol was in place to routinely identify and manage overweight/obese patients within each specialty
- b) if no protocol in place the reasons for this were sought
- c) if measurements of height and weight were routinely made
- d) the actions taken, by the clinician, if a patient was considered overweight/obese e.g. referral to dietitian etc
- e) whether it was felt that overweight/obesity affected outcomes or treatment within each specialty field
- f) attitudes to prescribing anti-obesity drugs.

Respondents who indicated they had a weight management protocol in place were asked to enclose a copy with their completed questionnaire

Two models of treatment were also suggested for possible development, Model A – to identify treat and manage overweight/obesity within each medical sub-specialty, or Model B to identify and then refer to a specialist obesity clinic (Appendix 1). Those surveyed were asked to indicate their preference.

4.3 Results

4.3.1 Pilot study

All pilot questionnaires were returned completed. Three respondents reported having a protocol in place but did not return a copy of this. Height and weight were routinely made in 55% of responses, referral to a dietitian was the preferred option if a patient was considered overweight, all agreed that overweight/obesity affected treatment outcomes. Model A was the model of choice for 44% of respondents.

None of the respondents suggested the addition or omission of any questions. Thus it was felt that the questionnaire was acceptable, and the questions unambiguous. No changes to the questionnaire were made in light of the pilot.

4.3.2 Main Survey

The overall response rate was 55%, response by specialty was: endocrinology 2%, orthopaedics 11%, obstetrics and gynaecology 11%, cardiology 2%, general medicine 12%, respiratory medicine 3%, general surgery 14%. Only 9% (5) of respondents reported having a protocol in place for the management of patients who were overweight or obese, (diabetes/endocrinology, renal medicine, general surgery, cardiology). However, none of the clinicians enclosed a copy of their protocol with their completed questionnaire.

4.3.3 Reasons for having no current protocol for weight management

Overall, the opinion of 51% of respondents was that weight management (including obesity treatment) should be undertaken by a specialist service either run by general practitioners, or by clinicians in a secondary care setting (Table 4.1). Lack of expertise and inaccessibility to expertise were cited frequently as reasons for having no protocol in place.

Twenty two percent of responding clinicians felt that weight/obesity management was not important to health care in general (gastroenterology, general medicine, general surgery, obs/gyn, cardiology) or not important to their specialist area (gastroenterology, respiratory, colorectal surgery, breast/general surgery, urology, thoracic surgery).

Other specific reasons for not having a protocol in place included:

“not aware that specialist advice/treatment is necessary for weight loss”

“over-weight is the responsibility of the patient”

“previous attempts at a weight management strategy in a general surgery context has often proved fruitless, we now just get on with it”

“waiting times to see dietitian, and I find that most patients attending dietitian are not motivated enough to lose weight”

4.3.4 Recording of height and weight

Both height and weight were reported as being routinely recorded in outpatient clinics in just over half the responses (52%). Weight only was measured in a further 5% of cases. The outpatient clinics not measuring height and weight, and so unable to calculate body mass index, included: orthopaedics, general surgery, obs/gyn, gastroenterology, respiratory medicine, general medicine, colorectal surgery, upper GI surgery, cardiology, and urology.

4.3.5 Action taken by the clinician if they considered a patient to be overweight/obese

Overall, if a patient was considered overweight or obese, referral to the hospital dietitian was the most frequently selected option (Table 4.2), and included the clinicians who reported having a protocol in place, and also those who did not routinely measure patient’s height and weight. Among those who selected this option, 25 indicated that this would be their only course of action, while 10 indicated that they may also refer a patient back to their GP for treatment. Very few clinicians said that they would take no action. Referral to a specialist obesity physician was not considered by any of the clinicians.

Almost all consultants (94.4%) agreed that overweight/obesity affected outcomes and treatment within their area of expertise. This included all those who said that weight/management was not a priority for health care in general, and the majority who said it was not important to their specialist area (71.4%).

About one in five consultants responded that they were happy to prescribe anti-obesity drugs, however 81.5% said they would not currently be comfortable prescribing them within their own specialist practice. A number of reasons were given for this, the most frequently cited being lack of experience in the use of these drugs. Other reasons for not using these drugs included:

“patients’ need to consume less calories not take drugs at the NHS’s expense, does not treat the cause of obesity which is a basic arithmetic problem – calories in > than calories out”

“no confidence in these methods, believe lifestyle modification is the cornerstone of management and anti-obesity drugs should be dealt with by a specialist”

“patients’ treated with drugs would need follow-up and I cannot follow-up patients for weight management purposes alone”

“I do not have the time or inclination to manage obesity within my specialty”

About twice as many clinicians chose Model B (identify and refer to a specialist obesity clinic) than Model A (identify treat and manage overweight/obesity within each medical sub-specialty) as the model for potential development (64% v 31%, $p < 0.0001$, χ^2 test). Two consultants wanted neither model the additional comment from one being “no evidence either would work – waste of money”. On the other hand the view of another consultant was that “either model would represent an improvement, however, what was the evidence for either, and perhaps A, or B should be a locally performed trial”.

4.4 Discussion

It is forecast that by the year 2010 one third of UK adults will be clinically obese (Williams, 1999) and the costs to health care services are expected to rise to an estimated £3.6 billion (NAO, 2001). The contribution of overweight to type 2 diabetes and metabolic syndrome is such that weight gain is overtaking smoking as a cause of coronary

heart disease and cancers (House of Commons Health Committee 2004). The development of strategies for the prevention and treatment of obesity is now a high priority. Primary care is usually identified as the most appropriate setting for weight management (SIGN 1996, R Coll Phys 2004, NICE 2006) and there is little NHS activity related to the management of obesity outside general practice (NAO 2001). Previous research has shown that obesity is common in many different outpatient clinics (Cleator *et al.*, 2002), and contributes to pathology and distress in many ways.

The present survey showed clearly that most hospital specialists recognise that obesity is contributing to their patients' ill health, but suggests that they perceive little value in weight management. This is at odds with the literature and may reflect the unrealistic goals of obese patients to become thin. Five to ten percent weight loss brings multiple health benefits (Goldstein, 1992) and is now an internationally accepted target for the short-term weight loss phase of weight management (SIGN 1996, NIH 1998, R Coll Phys 1998, NICE 2006). Taking the example of type 2 diabetes alone, which now affects 5-10% of all 60 year olds (SEDH 2000) and as much as 20-30% of older Asian groups (McKeigue *et al.*, 1998), 5-10% weight loss with diet and exercise will reduce new diabetes by 58% over 4 years (Tuomilehto *et al* 2001, DPP 2002). The addition of orlistat – a non-absorbable anti-obesity agent – reduces new diabetes by a further 38% over 4 years (Torgerson *et al.*, 2004). Modest weight loss also improves lung function, reduces the frequency of sleep apnoea, alleviates osteoarthritis and improves ovarian function (WHO 1998). There are strong arguments for urging clinicians to incorporate weight management within their specialty practices.

Clinicians who reported having a formal weight management protocol in place were in the minority. None forwarded a copy of the protocol suggesting that it may not in fact be

documented or formalised. The usual course of action taken by these clinicians if a patient was considered overweight/obese was referral to the hospital dietitian.

Most clinicians felt they could not currently provide weight management within their areas of specialisation and just over a quarter indicated that they would refer patients back to their own GP for weight management. However previous research has shown that GPs also feel that they do not have the expertise or resources to manage obesity/overweight (Hankey *et al.*, 2004). Training is clearly an issue as clinicians feel they do not have the necessary skills to treat those who are over-weight/obese and it is acknowledged that “little has been done to expand nutrition into the core training of all health professionals” (R Coll Phys, 2004).

Identifying those who are overweight/obese is a crucial step in its management, and secondary care clinics are considered a good opportunity to identify patients (Cleator *et al.*, 2002). In the present study almost half of clinicians reported that height and weight were not recorded routinely at their clinics. Therefore the opportunity to identify and manage those who are overweight/obese is, in many cases, lost. Lack of expertise and or access to expertise was commonly cited as a reason for not having a protocol in place. This may discourage clinicians from taking time to identify overweight/obese patients if they feel that effective management is not accessible or available.

There are clearly different ways forward. Most clinicians favoured Model B, (identify and refer to specialist obesity clinic), for potential development. However a third of respondents felt that they could valuably tackle obesity within their specialist practice. A low cost approach, by using staff and resources already available within each specialty, would be to build on this substantial minority. The comment of one clinician that evidence for the development of either model was lacking and research was needed is pertinent.

Since there is no established model of best practice in specialist secondary care of obesity in routine NHS services (as distinct from isolated academic units) the best plan is to establish programmes on the basis of best available evidence, but with a closed-loop audit to permit improvements to be incorporated. This needs to be established on the background of better incentives to enhance the first-line management of obesity in primary care –e.g. Counterweight (Counterweight Project Team, 2004b). A specialist obesity service is about to be piloted within the Greater Glasgow Health Board area and will provide much needed evidence for the development of effective obesity management strategies in routine clinical care.

4.4.1 Limitations

The present study was limited both geographically and in terms of the survey numbers. The response rate may also be considered inadequate, increasing the potential for non-responder bias. Previous research regarding response rates to postal questionnaires amongst health professionals, including hospital consultants found that response rates varied from 58-83% (Cartwright, 1978). However, it is thought that bias can occur even with high response rate (Barclay *et al.*, 2002). In the present survey it is possible that equal numbers of non-responder were passionate for and against weight management. The consensus amongst a wide range of hospital specialists suggests that the views reported may reflect those nationally.

4.5 Conclusion

Effective prevention and management are required to challenge the obesity epidemic. This will require the involvement of both primary and secondary care NHS settings. This study has provided a partial answer to research questions 3, 4, and 5:

RQ3 Are formal protocols to routinely identify and manage overweight/obese patients in place in secondary care clinics?

RQ4 Is height and weight routinely measured in secondary care clinics?

RQ5 What steps are taken to manage patients who are identified as overweight or obese?

NHS secondary care consultants are clearly concerned about obesity and its impact on their specialty field. Most have no clear strategy and would like one (RQ 3). The opportunity to identify patients who are overweight or obese is frequently missed as height and weight are frequently not measured (RQ 4). Some consultants are willing to take on weight management, but others are ignorant of its value and remit. While acknowledging the adverse effects of obesity in clinical practice, many clinicians still regard this as an area for which they feel unskilled and are under resourced (RQ 5). It is encouraging that, despite this, about one third of all consultants felt prepared to incorporate obesity and weight management within their routine specialist practice.

This part of this thesis would be considered Phase 2 Translational Research (Lean *et al.*, 2008). It uses mainly a quantitative approach, with some qualitative aspects. The results indicate that the efficacious and safe methods developed for weight management (including, for example the dietary intervention reported in Chapter 5) still need to be presented and evaluated in routine secondary care practice, if they are to be effective and sustainable. This study did not ask about the use of obesogenic drugs (Chapter 3) but that would be one issue which secondary care consultants cannot ignore ethically as many of their patients are likely to be prescribed one or some of these drugs.

Table 4.1 Reasons for not having a formal weight/obesity management protocol

Reasons	n (%)*
Weight/obesity management not a priority for health care in general	5 (9.1)
Weight/obesity management not important to this specialist area	7 (12.7)
Expertise not available to treat weight/obesity management within this specialist area	21 (38.2)
Personnel skilled in weight management inaccessible	13 (24.0)
Weight/obesity management best undertaken by dedicated secondary care obesity specialist service	13 (23.6)
Weight/obesity management should be undertaken by a GP specialist service	15 (27.3)
Other	11 (20.0)

*Column greater than 100% as more than one reason could be given per person

Table 4.2 Current management if patient considered overweight/obese

Management	n (%)*
Refer to hospital dietitian for your area	40 (74.4)
Refer to clinical nurse specialist	1 (1.9)
Refer to obesity specialist physician	0 (0.0)
Refer back to GP for management	15 (27.8)
Refer to commercial slimming organisation	2 (3.7)
No action	3 (5.6)
Other referral	9 (16.7)

*Column greater than 100% as more than one option could be chosen

Chapter 5

Influence of red meat consumption on iron status in dieting pre-menopausal women

5.1 Introduction

The prevalence of obesity has risen significantly over the last decade and with it the already huge numbers of women attempting to control their weight. Young women often have poor iron status (NDNS 2004, vol 4, SHS 2003), and habitual dieting is reported to have a negative effect on iron stores (Houston et al., 1997). In Europe and the USA, while diet alone is seldom the cause of iron deficiency (Frewin et al., 1997) poor dietary intake is not an uncommon contributory factor (Goddard et al., 2005). Red meat is an important source of iron in its most bio-available form haem iron (Rossander-Hulthen., et al., 1996) (Table 5.1). Although haem iron is the most bio-available non-haem iron, found in cereals, fruit vegetables, roots and beans, is a significant source of dietary iron (Rossander-Hulthen & Hallberg 1996). Absorption of haem iron is between 15-40% of intake while absorption of non-haem iron is lower at 2-20% of intake (Ball et al., 1999, Hunt, 2003). The reference nutrient intake (RNI) for iron in women is 14.8 mg per day (COMA). However national survey data shows that in the UK women consume only around 10mg of iron per day from food sources and that 40% of younger women have iron intakes below the lower reference nutrient intake (LRNI) (NDNS 2004, vol 5).

In the UK around 12% of the population are estimated to be either vegetarian or avoid consuming red meat (Harvey *et al.*, 2005). The dietary iron in vegetarian diets is less bio-available than non vegetarian diets because of reduced meat intake and an increased consumption of plant based inhibitors of iron absorption (Hunt, 2003).

This project was designed to:-determine the effect on body weight and iron status in women of a programme of weight loss and maintenance, which includes the regular consumption of red meat in comparison to one that excludes it. The hypothesis to be tested was that the inclusion of red meat in a weight reduction diet on at least 5 occasions per

week would protect iron status to a greater extent than a weight reduction diet that excluded it.

The study was devised to address the following research questions:

RQ6 Does a weight reduction diet, that regularly includes lean red meat, maintain iron status in pre-menopausal women?

RQ7 Does a weight reduction diet, which excludes lean red meat, maintain iron status in pre-menopausal women?

RQ8 Does the effects on iron status differ between treatments?

5.2 Methods

The study design, setting and data analysis have been described in Chapter 2 (Methods).

5.3 Results

5.3.1 Recruitment

Recruitment commenced in April 2005. Within the first month it was evident that the response to the study advertisement was poor and that the ferritin exclusion criteria initially set by the Research Ethics Committee made eligibility difficult. Application was made to the Ethics committee on 26th April 2005 to extend the upper level for serum ferritin to 20ug/l and this was approved.

It was also felt that potential volunteers were reluctant to approach the study researcher in person in front of colleagues within their worksite. A mobile telephone was purchased and recruitment posters amended to include the telephone number. This allowed volunteers to contact the researcher privately to discuss participation. Application was also made to the ethic's committee to extend recruitment to other worksites. Further worksites were then

identified and recruited via the Scotland's Health at Work initiative (www.healthyworkinglives.com). Recruitment continued until the end of May 2006.

One hundred and sixty women, from 12 separate worksites, volunteered to participate in the study. The mean age of volunteers was 42 (SD 7.4) years and mean BMI was 31.9 (SD 4.8) kg/m². In three cases it was not possible to obtain a blood sample to determine baseline serum ferritin or haemoglobin. Fifty eight percent of volunteers (n=93) had a serum ferritin level greater than 20 and were therefore ineligible to participate. In 26 cases (16%) the serum ferritin levels were below the 10ug/l level, imposed by the ethics committee, and were therefore excluded. All of these women were informed that their ferritin levels were low and advised to visit their general practitioner to discuss their results. Blood results were forwarded to each general practitioner.

Thirty-eight women (23.7%) fulfilled the inclusion criteria and were eligible to participate. Following baseline screening one woman decided not to participate and another was started on iron supplements by her general practitioner. In total 36 women entered the randomised controlled study.

5.3.2 Attrition

Six subjects (4 meat group, 2 no meat) withdrew their participation, 5 during the initial 12-week weight loss period and one during the weight maintenance period. The reasons given for withdrawal were:– unable to continue excluding red meat, not willing to include red meat in line with study protocol, not following eating plan, too many things going on in their personal life. In two cases it was not possible to elicit the reason for withdrawing as both women failed to respond to any form of contact.

5.3.3 Study Power

Original sample size calculations indicated that a study based on **25** analysable patients per group (i.e. **33** recruited per group allowing for 30% dropouts) would have power of 80% to detect as statistically significant a difference between the baseline to week 24 changes in the two study groups of 6.8 units in serum ferritin and would represent a clinically meaningful improvement. In the current study, despite 14 months recruitment and considerable extra commitment of time and unfunded resources, this was not achieved.

The achieved sample of 30 subjects provided 80% power to detect or exclude a difference in the mean changes in serum ferritin between the meat and no meat groups of 8.3 units, rather than 6.8 units. Alternatively, 30 subjects gave 63% power to detect the difference of 6.8 units specified in the original protocol.

5.3.4 Baseline Measurements

The 36 subjects were randomised to 2 groups, 19 to the meat group and 17 to the no-meat group. Following randomisation the physical characteristics of the two groups were similar (Table 5.2). Serum ferritin levels were <15ug/l in 11 women (30%), one woman had a haemoglobin level <12g/dl. A significant difference in baseline serum ferritin observed between the meat and no meat groups respectively 17.0 (SD 2.3) vs. 14.5 (SD 3.5) ug/l p=0.02.

Fifteen women (41.6%) described their menstrual bleeding as either heavy or very heavy.

5.3.5 Baseline Dietary Habits

The dietary habits of the two diet groups were broadly similar at baseline. Around 50% of both groups consumed fruit less than once a day with around one third of each group eating fruit only 2 to 4 times per week (Fig 5.1). More participants in the no-meat group

consumed vegetables daily at baseline in comparison to the meat group (Fig 5.3 & 5.4). In both groups the majority of participants consumed red meat 2 to 4 times per week (Fig 5.6). A similar picture was seen for consumption of poultry (Fig 5.7). Around 30-40% of both groups consumed white fish at least once a week, however 40% of those in the meat group did not eat white fish at all (Fig 5.8). The majority of those in the no meat group did not eat oily fish at all compared to only one-third of the meat group (Fig 5.9). Consumption of potatoes, rice or pasta was low in both groups with only 30-40% of participants in each group eating these carbohydrate rich foods once a day (Fig 5.11). In both groups high fat and sugary foods were eaten regularly (Figs 5.12 -5.16). White bread was the bread of choice in almost half of participants in both groups at baseline (Table 5.7).

5.3.6 Energy Prescription

Daily energy prescriptions ranged from 1200 to 1700 kcal/day. Thirty percent of participants were prescribed 1300 kcal per day.

5.3.7 Serum Ferritin

An increase in serum ferritin between baseline and week 24 was observed in both diet groups. When the data were examined for the groups combined this rise was significant, +3.24 (SD 9.02) ug/l $p=0.03$. However within group increases did not reach statistical significance (Table 5.3). Although the mean increase in serum ferritin was greater in the meat consumers, between-group analysis showed no significant differences in the changes in serum ferritin (Table 5.3). Similarly no between group difference was evident in mean serum ferritin concentrations at week 24 (Table 5.4).

However while iron status did not deteriorate as people lost weight there is some suggestion ($p = 0.07$), that in patients allocated to the meat diet, better adherence to dietary advice, with greater weight loss, led to greater improvements in serum ferritin (Fig 5.17). The inclusion of red meat provides greater dietary variety and may have facilitated improved adherence with dietary advice.

5.3.8 Weight Change (0-12 weeks)

Analysis showed a reduction in mean weight from 78.4 (SD 11.1) kg at baseline to 75.6 (SD 11.8) kg at week 12, $p < 0.0001$. Within group reductions in weight were significant, 2.8 (SD 1.9) kg, $p < 0.0001$ in the meat group, and 2.6 (SD 2.4) kg, $p < 0.0001$. Comparative analysis showed no difference in weight loss between those who included meat in their diet and those who excluded it $p = 0.69$.

Reductions in weight were mirrored by reductions in waist circumference in both the meat and no meat groups respectively -3.2 (SD 3.4) cm $p = 0.001$ and -3.5 (SD 3.0) cm $p < 0.0001$. No between significant group differences were seen in mean waist reduction.

Of those who completed the weight loss period ($n = 31$) all, except one, lost weight. Mean percentage weight loss was 4.2 (SD 2.7) %, $p < 0.000$. Of the 30 women who lost weight 20 (67%) lost 0- 5% of initial body weight. Ten women (33%) achieved between 5 and 10% weight loss. Comparison between the meat and no meat group respectively showed no difference in terms of percentage weight loss 4.5 (2.2) vs. 3.8 (3.2)% $p = 0.50$.

5.3.9 Weight Maintenance (12-24 weeks)

Thirty subjects completed the full 24-week programme. Mean weight gain in those who completed the programme was +0.22 (SD 1.3) kg, $p = 0.37$ with no significant between group differences seen, meat +0.28 (SD 1.4) kg, no meat +0.17 (SD 1.3) kg, $p = 0.83$.

5.3.10 Dietary Habits

Weight loss period (0-12weeks)

Significant improvements were seen in the dietary habits of subjects. Over 90% of subjects in both diet groups increased their intake of fruit and vegetables during the weight loss period. In both groups the majority of participants consumed ≥ 5 portions of fruit and vegetables per day.

Similarly the majority of subjects in both groups increased their consumption of potatoes, rice, pasta and breakfast cereal. Two thirds of both groups consumed breakfast cereal every day of the week, and the majority of both groups ate potatoes, rice or pasta daily (75-93%).

No between group differences were seen in the proportion of participants changing favourably their intake of these food groups during the weight loss period (Table 5.5).

Frequency of bread consumption remained largely unchanged, however at week 12 the majority of subjects in each group consumed brown, granary or wholemeal bread instead of white bread (Table 5.7).

Between group differences were seen in the proportion of subjects increasing their consumption of both white and oil rich fish. More subjects in the no-meat group increased their consumption of these foods (Table 5.5). At week 12, 46% of those in the no meat group were consuming white fish between 2 and 7 times per week. A significant proportion of subjects in the no meat group increased their consumption of poultry however no significant between group difference was observed.

A significant number of subjects in the meat group increased their consumption of red meat during the weight loss period ($p=0.003$, sign test) from 3 times per week at baseline to 5-7 times per week.

A significant proportion of subjects in both groups reduced their frequency of consuming sweets, chocolates and savoury snacks (Table 5.5). The proportion eating sweets on a daily basis fell to 21% from 37% in the meat group and from 29.5 to 6% in the no meat group.

Weight Maintenance period (12-24 weeks)

Overall the improvements in diet observed at the end of the weight loss period were maintained throughout the weight maintenance period. However, a significant proportion of subjects in the meat group decreased their consumption of fruit and vegetables (Table 5.6), 40% of women ate fewer than 5 portions per day.

Dietary assessment in the present study was performed using a food frequency questionnaire and not weighed intake diaries. A limitation of the study is that it was not possible to make accurate calculations of dietary iron intake. However taking a 1300 kcal eating plan as an example (Appendix 6), it was we estimated that potential availability of dietary iron was approximately 28.6 and 27.6mg/d for the meat and no-meat group respectively, with the majority being non-haem iron. These figures could vary widely depending on individual food choice, the consumption of inhibitors and enhancers of iron absorption and compliance with portion advice.

5.4 Discussion

A widespread belief that red meat is “high in fat” means that for many, self directed attempts at “dieting” are characterised by the exclusion of red meat from their diets (Houston *et al.*, 1997). However red meat is an important source of iron in its most bio-available form (Rossander-Hulthen & Hallberg 1996) and its exclusion from the diet may be a contributory factor in the prevalence of iron deficiency, especially in young women. Previous research has shown that “reducing fat and cholesterol intake” are frequently cited as reasons for not eating red meat (Houston *et al.*, 1997). The Scottish Diet Report (1993) stresses that while consumption of “meat products” needs to be reduced because of their very high saturated fat content, consumption of red meat itself need not be reduced on nutritional grounds. Previous research has shown that in terms of weight loss and improvements in plasma lipids the elimination of red meat from the diet is unnecessary (Leslie *et al.*, 2002, Watts *et al.*, 1988).

The prevalence of iron deficiency in the present study was greater than reported for the female Scottish population, with 16% of volunteers ineligible to participate because of iron deficiency. These data indicate that iron deficiency is under-recognised and untreated in the Scottish female population.

The number of volunteers within each worksite was low. This was in contrast to previous dietary/weight management studies carried out by this department in a worksite setting, which have attracted a large number of volunteers (Leslie *et al.*, 2002). A recent review of worksite interventions reports that program/initiatives that rely on individual motivation alone are likely to be less successful than programs that also include environmental strategies (Goetzel 2008). While the worksites/employers that participated in the present study were supportive they were not actively involved in promoting the initiative and no

additional environmental interventions were run by the worksites in parallel to the present study. This may have contributed to our low volunteer rate as employees may perhaps felt their employers were not wholly supportive of their participation in the study.

The low recruitment rate combined with the higher prevalence of iron deficiency in our volunteers were significant factors in the non-achievement of the intended study numbers. The women excluded because of low ferritin were not symptomatic, but there was concern from the Ethics Committee that dietary intervention could provoke anaemia. The results of this study suggest that both diets actually improved iron status, so excluding subjects with ferritin <10ug/l was unfortunate.

Attrition from weight management studies can be high (Honas *et al.*, 2003, Rossner, 1992), and was anticipated to be around 30% in the present study. However the attrition rate was low at just under 17%. Low attrition is thought to be an indicator of some success and it is suggested that programs with low attrition rates will be successful (Rossner, 1992). The low attrition rate in the present study suggests that compliance with the eating plans was not difficult for participants. Compliance is a key issue in weight management and may not only optimize weight loss, but lead to long-term changes in dietary habits, thus improving the likelihood of maintaining weight loss and improving long term health.

Given the low attrition rate found in the present study, had the prevalence of iron deficiency in our population sample been lower, the required study numbers could potentially have been achieved.

At baseline just under one-third of participants in the present study fulfilled the criteria for iron depletion and were therefore at higher risk of iron deficiency. A significant between group difference in serum ferritin was observed at baseline, however as participants had

been randomly allocated to the treatment groups this difference can only be attributed to chance (Burgess *et al.*, 2003).

Pre-menopausal women are susceptible to iron deficiency anaemia due to the demands of pregnancy and menstruation on their smaller iron stores. Previous research has found that ferritin status is inversely related to menstrual blood loss – higher blood loss leading to lower ferritin levels (Harvey *et al.*, 2005). In the present study just over 40% of participants described their monthly blood loss as either heavy or very heavy, again increasing their risk of developing iron deficiency anaemia.

Improvements in serum ferritin, from baseline to week 24, were observed in both diet groups over the study period. Haem iron is the most bio-available of the two forms of dietary iron with 20-25% absorbable compared with 1-5% of non-haem (Hercberg *et al.*, 2001). Red meat is a rich source of haem iron and its presence also enhances the absorption of non-haem iron (Cook, 1976). Other protein sources such as poultry, white and oil rich fish are also important sources of haem iron (McCance & Widdowson 2002) (Table 12) and the capacity to enhance the absorption of non-haem iron is also found, although to a lesser extent, with these foods (Cook, 1976) . In the present study consumption of haem iron was increased in both diet groups.

Non-haem iron, found in cereals and fruit vegetables is also a significant source of dietary iron (Gregory *et al.*, 1990). Since the late eighties however the contribution from meat, meat products, fish and poultry to iron intake has decreased to around 16% from 21% (MAFF 2000). It is therefore non-haem iron that provides the bulk of dietary iron (Gregory *et al.*, 1990). The dietary advice given in the current study was designed to provide around 50% of total energy from carbohydrate, much of which was provided by

bread and cereal products. Consumption of these foods was increased in both diet groups. The consumption of fruit and vegetables also increased in the study population and it can be assumed that a variety of fruits were eaten including those rich in ascorbic acid, which is known to enhance the absorption of non-haem iron (Rossander-Hulther & Hallberg 1996, Monsen 1988) .

The improvement in ferritin concentrations, seen in both diet groups, reflects both groups consuming a healthier balanced diet that was richer in both haem and non-haem iron. However, the rise in ferritin in both groups may also, in part, reflect regression to the mean (RTM), as subjects were recruited on the basis of low ferritin. Approaches to reduce this effect include random allocation to comparison groups (Barnett *et al.*, 2005). Random allocation ensures that RTM effects should be the same in all groups. The inclusion of a placebo group allows an estimate of the RTM effect. In the present study participants were randomly allocated to one of two dietary groups, however this study did not include a placebo group. Another approach to minimise RTM is the use analysis of covariance (ANCOVA) (Barnett *et al.*, 2005). This adjusts participants follow up measurements according to their baseline value. In the present study changes in serum ferritin were analysed using ANCOVA. The use of both these approaches may have lessened the RTM effect.

The available data do suggest that the meat diet may be better. Although differences in serum ferritin were not significant at week 24, during the weight maintenance period, (week 12 to 24), ferritin continued to rise in the meat group while, in contrast, tended to fall in the no meat group. Whilst improvements in dietary habits were in general maintained during this period, in both groups the majority of subjects reduced their intake of fruit and vegetables therefore lowering their intake of Vitamin C, a known enhancer of

non-haem iron. The continued rise in serum ferritin levels in the meat consumers suggests a benefit from regular meat consumption in that it compensated for the fall in fruit and vegetable consumption, and the fall in serum ferritin observed in the no meat group was prevented. Additionally the 95% confidence intervals for the change in ferritin at week 24 were wide, and this does not allow us to exclude the possibility of a moderately large difference in favour of the meat diet.

However as the present study was underpowered it is not possible to draw definitive conclusions from these data. Previous research has reported a positive correlation between red meat consumption and serum ferritin levels, and proposed that this was due to the increased availability of haem iron (Cade *et al.*, 2005). Other research has found that women eating a diet rich in haem iron were found to have the highest serum ferritin levels, and red meat is the richest source of haem iron (Leggett *et al.*, 1990). It is also important to note that the eating plans used in the present study were designed to optimise nutrient intakes, including iron, and iron status may have been preserved because of a compensatory increase in the consumption of other dietary sources of iron. The eating plans were therefore likely to be nutritionally superior to those of self-directed slimmers. The elimination of red meat as part of slimming plans without concomitant dietary improvements may well deplete iron stores and contribute to iron deficiency and anaemia.

The achieved weight loss was similar in both groups and there would appear to be no differences in acceptability or compliance. The healthiest way to achieve weight loss is by following a balanced diet in which no food group is restricted or eliminated (NICE 2006).

Anecdotally many of the women in the no meat group reported that they were looking forward to including meat in their diet once the study period was over. Its inclusion provides a more varied diet, a good source of iron and is part of a healthy balanced diet on which any weight reducing diet should be based.

The failure of any weight management programme is more often than not a failure of maintenance rather than failing to achieve some weight loss (Wadden *et al.*, 1989). In the present study no significant weight regain was observed amongst the participants in either diet group. Continued “therapist contact” is consistently reported as a factor in improving weight maintenance (Perri *et al.*, 1993). The weight maintenance data in the present study are likely to reflect the continued one to one contact. The apparent acceptability of the eating plans is also a likely contributory factor in the maintenance of achieved weight loss.

Worksites provide a promising location for future weight management interventions. Health promotion or occupational health personnel are in a position to target obesity and weight management and contribute to reducing the prevalence of obesity and associated disorders. However in order to maximise uptake and success they should be initiated and promoted by management, with input from employees, and supported by environmental interventions (Goetzel *et al* 2008).

5.5 Conclusion

The presence of iron deficiency amongst our volunteers was higher than expected or reported by previous research and many of the women who were eligible to participate were iron depleted and therefore at increased risk of iron deficiency. These data are likely to reflect the poor dietary habits of our participants and the population in general. The present study provided answers to the research questions:

RQ6 Does a weight reduction diet, that regularly includes lean red meat, maintain iron status in pre-menopausal women?

RQ7 Does a weight reduction diet, which excludes lean red meat, maintain iron status in

pre-menopausal women?

RQ8 Does the effects on iron status differ between treatments?

Excluding red meat did not adversely affect iron status, and iron status improved in both groups over the study period. The eating plans used were designed to optimise nutrient intakes, including iron, and iron status may have been preserved because of a compensatory increase in the consumption of other dietary sources of iron. However the data, although not definitive, do suggest improvements in iron status from prolonged regular consumption of red meat (RQ 8). A larger study over a longer time frame would be required to produce data to support definitive advice for health promotion. The inclusion of red meat provides a more varied diet and remains a rich source of dietary iron, which should be included as an option in any healthy balanced diet for weight loss or stability.

Table 5.1 Iron content of commonly consumed sources of animal protein

Source (cooked)	*Fe (mg per 100g)	% Haem Iron (cooked)
Beef	1.4-3.6	78**
Lamb	0.7-2.6	70**
Pork	0.4-1.1	52**
Poultry	0.4-2.7	28**
White fish	0.1-1.2	20-40***
Oil rich fish	0.4-5.1	20-40#(uncooked)

Data from:-

*FSA (2002)McCance and Widdowson, The Composition of foods (6th Summary Edition): ** Lomabardi-Boccacia et al 2002: ***Rangan et al 1997: # Gomez-Basuaui & Regenstein 1992.

Table 5.2 Baseline measurements for participants randomised to the meat and no meat diet groups.

	Meat (n=19)	No Meat (n=17)	p
Age	41 (7.9)	41 (7.2)	0.88
BMI	29.9 (4.4)	30.1 (3.6)	0.89
Weight (kg)	78.8 (12.9)	78.0 (9.1)	0.84
Waist (cms)	98.2 (11.3)	94.9 (8.4.)	0.32
Serum Ferritin (ug/l)	17.0 (2.3)	14.6 (3.5)	0.02

All data expressed as mean and (SD)

Table 5.3 Mean (SD) for change in serum ferritin from baseline to week 24

Diet	Change in serum ferritin	S.E	95% CI	p
	ug/l			
Meat	+ 4.42 (10.7)	2.45	-0.74 to +9.56	0.08
No meat	+ 1.93 (6.7)	1.63	-1.54 to +5.41	0.11
Between group difference	2.48	3.02	-3.66 to +8.63	0.41

Table 5.4 Mean serum ferritin (SD) at week 24 by diet group and between group difference in serum ferritin at week 24 by ANCOVA adjusting for baseline differences.

Diet	Serum ferritin at week 24	S.E	95% CI	p
	ug/l			
Meat	21.42 (11.63)	2.67		
No meat	16.52 (7.84)	1.90		
Between group difference	+1.16	3.27	-5.49 to +7.83	0.72

Table 5.5 Number of subjects increasing/decreasing intakes of food groups during the weight loss period, and comparison of the proportion of subjects increasing/decreasing intakes by diet group

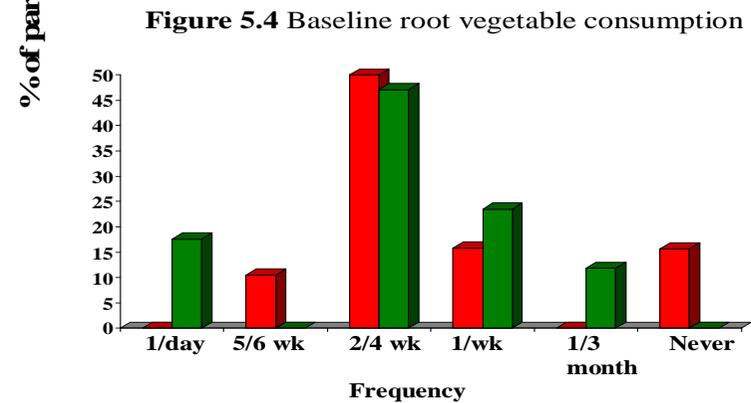
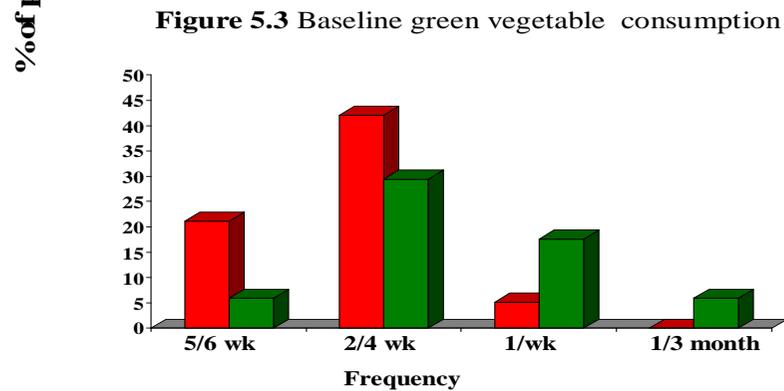
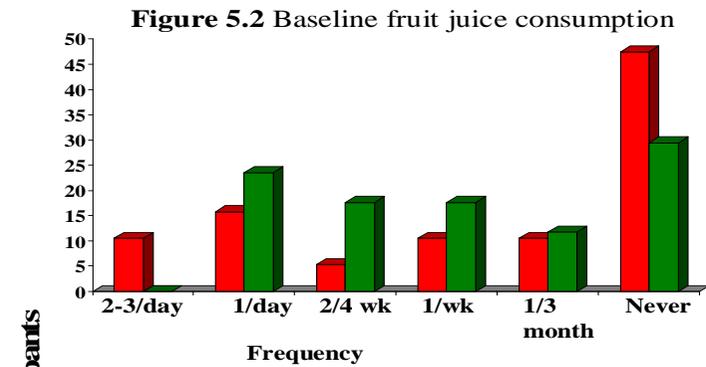
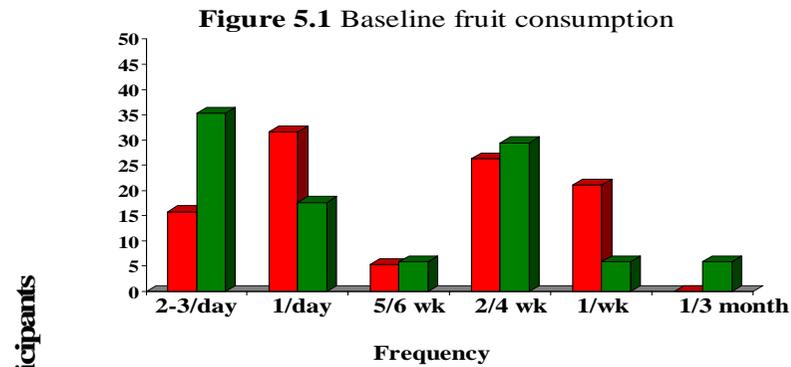
Weight Loss Period (0-12 weeks)							
	Decreasing	Same	Increasing	p (sign test)	Meat v no meat (Odds ratio)	95% CI	p
Potatoes, rice, pasta							
Meat	1	7	8	0.04	0.66	0.16 to 2.76	0.57
No meat	2	4	9	0.06			
Breakfast cereal							
Meat	1	7	8	0.04	1.1	0.27 to 4.68	0.85
No meat	2	6	7	0.18			
Fruit & vegetables							
Meat	1	0	15	0.001	1.0	0.06 to 18.8	0.96
No meat	1	0	14	0.001			
Oily fish							
Meat	4	9	3	1.0	0.13	0.26 to 0.72	0.02
No meat	0	5	10	0.002			
White fish							
Meat	5	9	2	0.45	0.52	0.008 to 0.33	0.002
No meat	2	2	11	0.02			
Poultry							
Meat	2	9	5	0.45	0.39	0.92 to 1.72	0.21
No meat	0	7	8	0.008			
Savoury snacks							
Meat	13	2	1	0.002	1.5	0.28 to 8.61	0.60
No meat	11	4	0	0.001			
Sweets/chocolates							
Meat	12	2	2	0.01	0.75	0.13 to 4.09	0.74
No meat	12	2	1	0.003			

Table 5.6 Number of subjects increasing/decreasing intakes of food groups during the weight maintenance period and comparison of proportion increasing/decreasing intakes by diet group

	Decreasing	Same	Increasing	p (sign test)	Meat v no meat	95% CI	p
Potatoes, rice, pasta							
Meat	2	11	1	1.0	1.0	0.12 to 8.21	1.0
No meat	2	11	2	1.0			
Breakfast cereal							
Meat	4	9	2	0.68	0.66	0.94 to 4.73	0.68
No meat	1	11	3	0.62			
Fruit & vegetables							
Meat	12	0	3	0.03	0.50	0.09 to 2.6	0.41
No meat	9	1	5	0.42			
Oily fish							
Meat	2	10	3	1.0	0.68	0.12 to 3.82	0.66
No meat	5	5	4	1.0			
White fish							
Meat	2	8	5	0.45	2.2	0.41 to 11.8	0.34
No meat	6	6	3	0.50			
Poultry							
Meat	2	12	1	1.00	1.00	0.57 to 176	1.00
No meat	5	9	1	0.21			
Savoury snacks							
Meat	3	8	4	1.00	1.6	0.23 to 11.46	0.62
No meat	1	9	4	0.68			
Sweets/chocolates							
Meat	4	8	3	1.00	0.42	0.15 to 3.49	0.69
No meat	3	9	3	1.00			

Table 5.7 Type of bread eaten at baseline and week 12 in both diet groups

	White		Brown, granary Wheatmeal		Wholemeal		Mixture		No usual type	
	Baseline	Wk 12	Baseline	Wk 12	Baseline	Wk 12	Baseline	Wk 12	Baseline	Wk 12
Meat group (n=19)	9 (47.4)	1(5.3)	7(36.8)	9(47.4)	1(5.3)	6(31.6)	2(10.5)	0	0	0
No meat group (n=17)	7(41.2)	1(5.9)	4(23.5)	5(29.4)	2(11.8)	8(47.1)	1(5.9)	1(5.9)	3(17.6)	0



Meat group (n=19) No meat group (n=17)

Figure 5.5 Baseline salad consumption

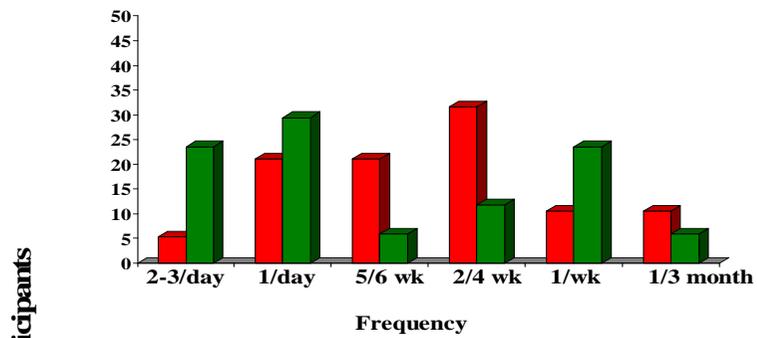


Figure 5.6 Baseline red meat consumption

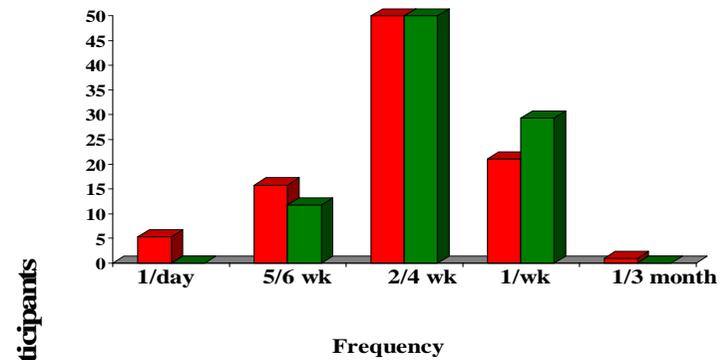


Figure 5.7 Baseline poultry consumption

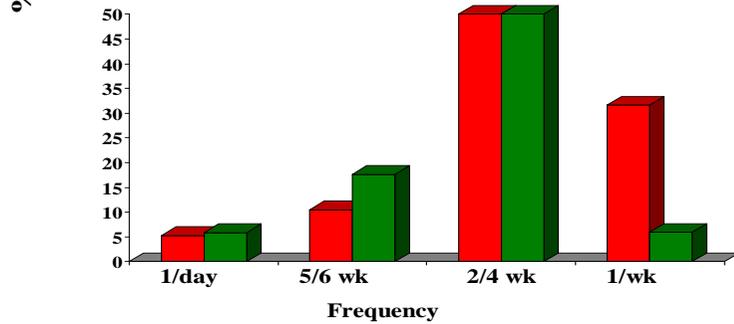
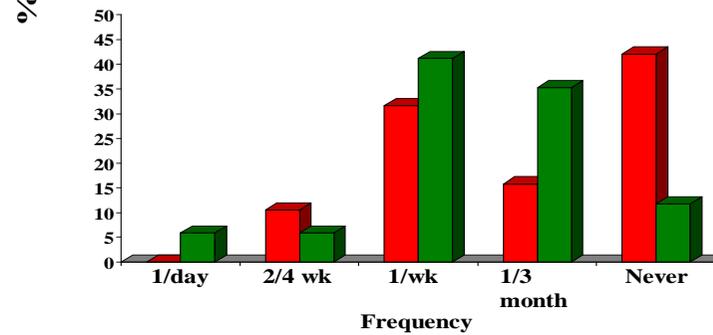


Figure 5.8 Baseline white fish consumption



Meat group (n=19) No meat group (n=17)

Figure 5.9 Baseline oily fish consumption

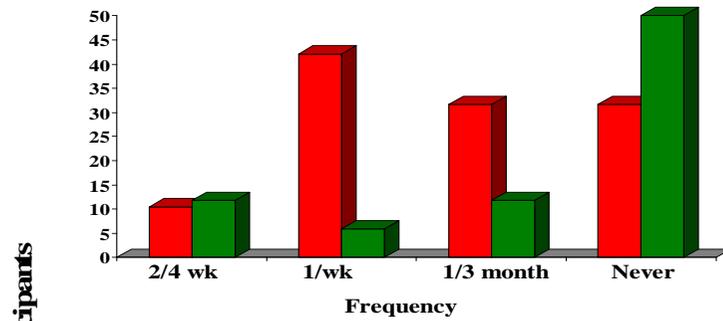


Figure 5.10 Baseline consumption of breakfast cereal

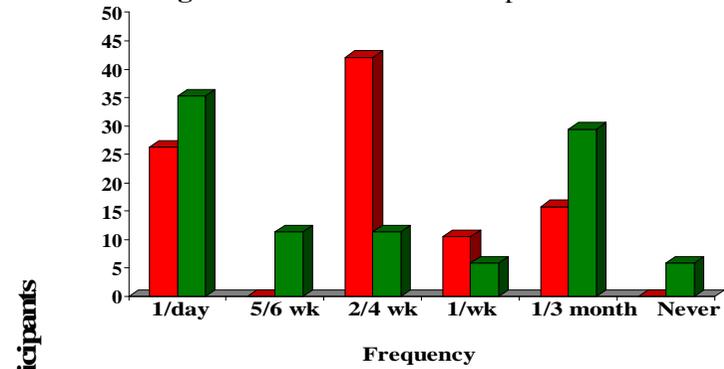


Figure 5.11 Baseline consumption of potatoes/rice/pasta

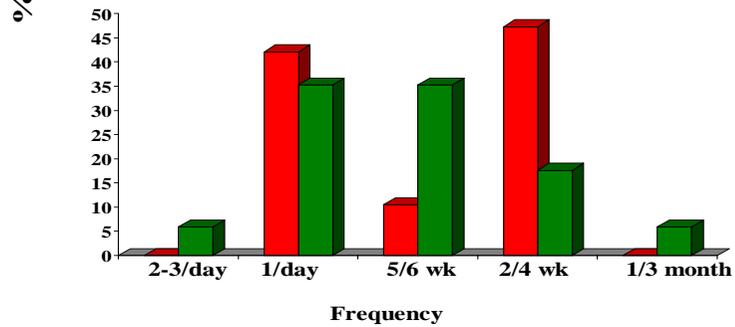
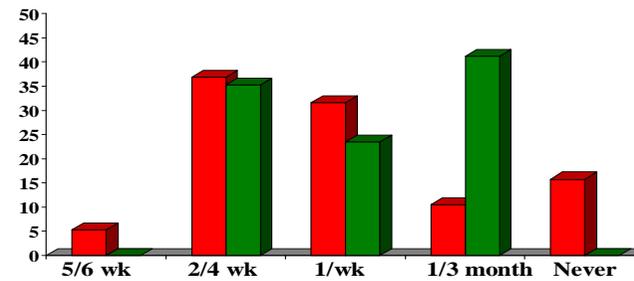


Figure 5.12 Baseline consumption of chips



Meat group (n=19) No meat group (n=17)

Figure 5.13 Baseline consumption of savoury snacks

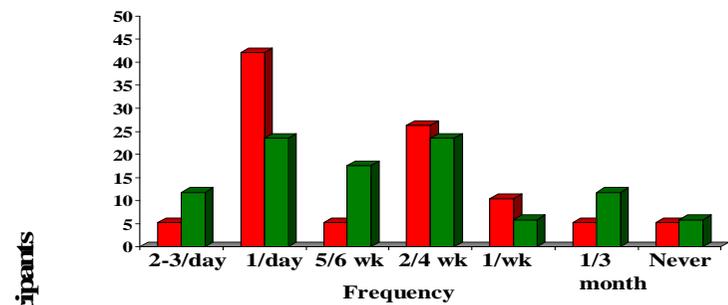


Figure 5.14 Baseline consumption of cakes/scones

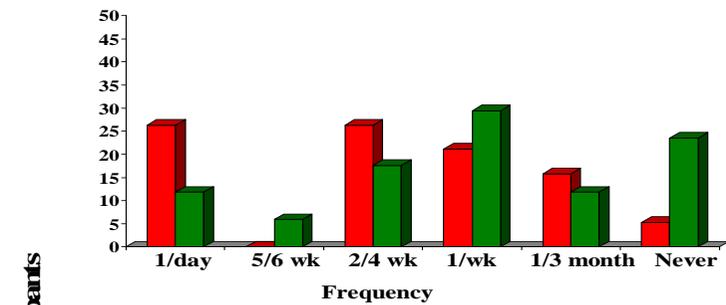


Figure 5.15 Baseline consumption of ice cream

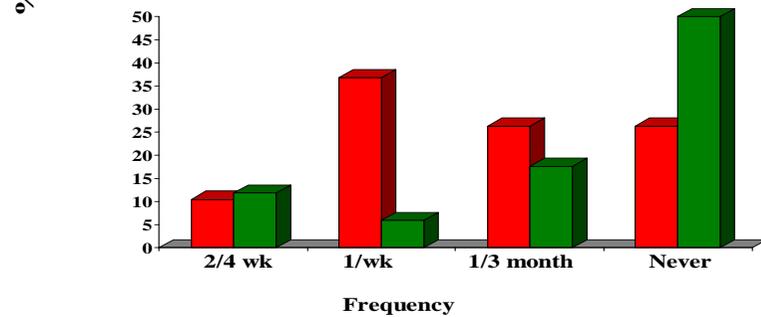
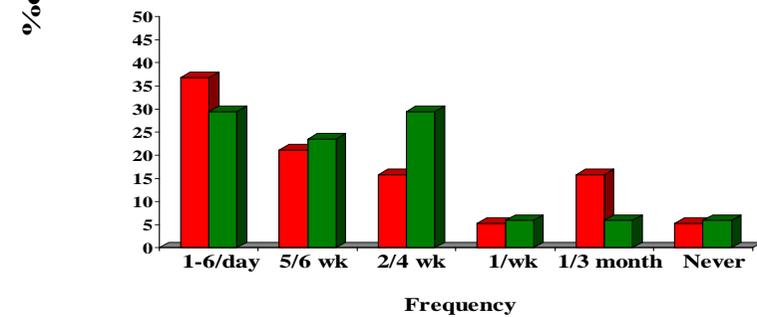
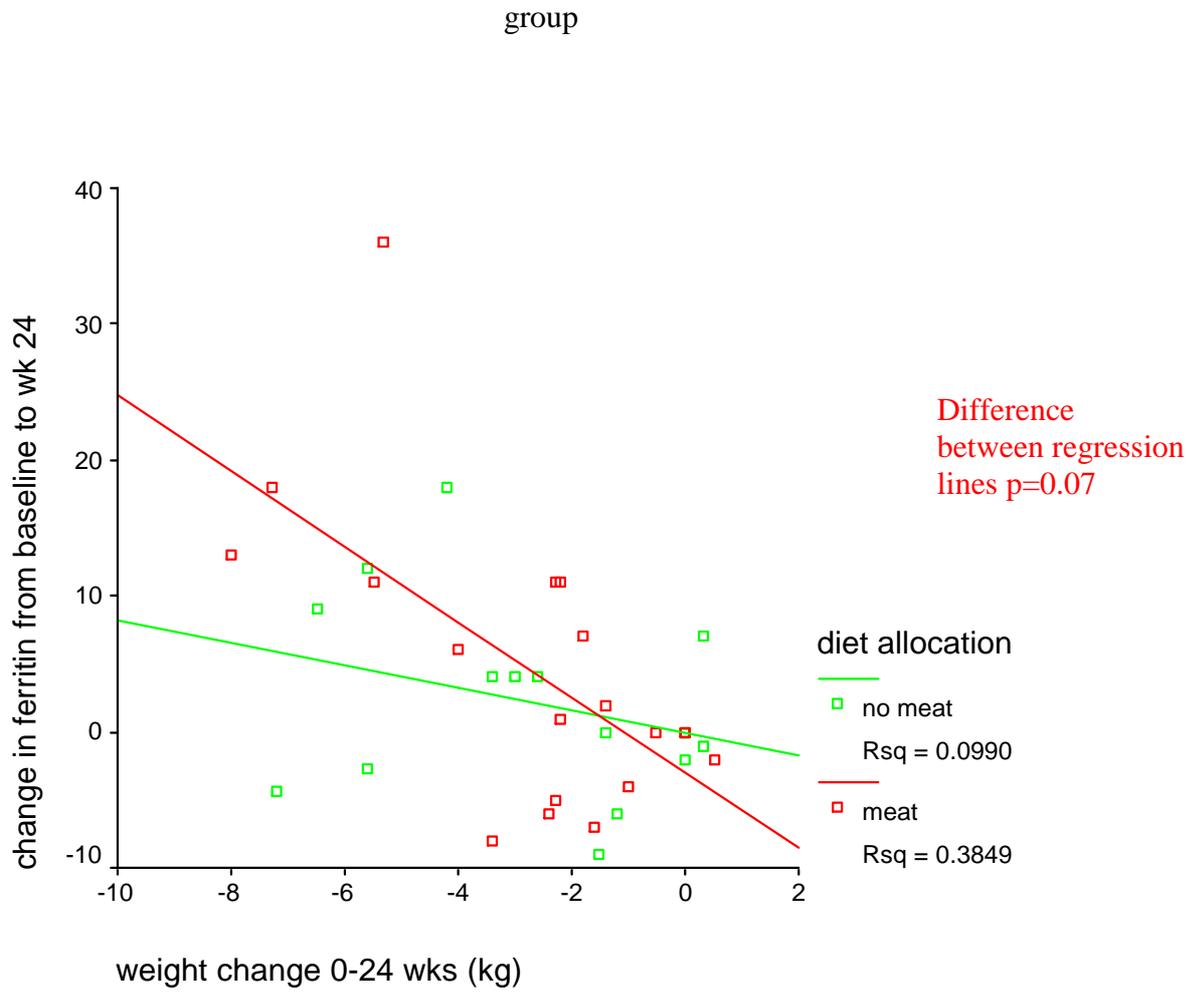


Figure 5.16 Baseline consumption of sweets & chocolates



Meat group (n=19) No meat group (n=17)

Figure 5.17 Relationship between weight change and changes in serum ferritin by diet



Chapter 6

General Discussion

6.1 Introduction

The health of the Western world is changing and many countries face a rising toll of death and disability from chronic non-communicable diseases. Many of the risk factors for these diseases are diet related and there are clear links with obesity. The development of strategies for the treatment and prevention of obesity is a priority for health promotion and education, and weight management guidelines have been produced by both government and professional bodies. However the management of obesity remains ad-hoc and fragmented with no concerted strategy in place in the UK or many other countries. The recent Foresight report (2007) stresses that all factors that contribute to the rising tide of obesity require to be recognised and addressed, and highlights the need for long term approaches utilising a wide range of interventions.

This thesis has investigated three factors associated with either the aetiology of, or the management/treatment of obesity:

- 1 the effect that some commonly prescribed drugs, used in the treatment of chronic non-communicable diseases associated with obesity, can have as an adverse effect on body weight,
- 2 current practice in secondary care clinics, where the management of non-communicable diseases associated with obesity and treated with drugs associated with weight gain is set, with regard to the identification and initiation of treatment for patients who are overweight or obese, and
- 3 which dietary approach for weight loss and weight loss maintenance would preserve iron status in pre-menopausal women, a group at increased risk of iron deficiency, who are identified as overweight or obese.

6.2. Research Questions and Answers

RQ1 Is weight gain an adverse effect of some commonly prescribed drugs?

RQ2 Is the effect on body weight reported and quantified in studies examining these drugs?

The research carried out as part of this thesis has provided evidence that drugs can contribute to weight gain especially those used to treat psychiatric disorders. Not all drugs associated with weight gain were included, however those that were are those consistently reported in medical/scientific literature and used to treat chronic non-communicable diseases.

About 15 million people are on beta-blockers often for conditions made worse by weight gain. Weight gain is clearly an important side effect whose importance is much greater in the 21st century than in the 1960's when beta-blockers were first introduced.

Similarly, most schizophrenic patients receive antipsychotic drugs. Prescribing has increased since the NICE recommendation of atypical antipsychotics as a first line option in the treatment of schizophrenia. In 2006-07 prescriptions accounted for two-thirds of all antipsychotic prescriptions. Half these patients could therefore expect a weight gain of between 3 and 10 kg. The potential for any side effect, including weight gain, should be discussed with patients at the commencement of treatment using any drug that is associated with weight gain. The use of alternative drugs may be possible and should be considered. However if this is not possible then all support should be available to help patients minimise the potential weight gain and related non-communicable diseases associated with obesity. The numbers in the population receiving treatment with drugs associated with weight gain has risen significantly and may rise further. Thus pharmacotherapy has become a significant factor in the continuing rising prevalence of obesity. Schizophrenia is now recognised as a high risk condition for obesity, type 2 diabetes and coronary heart disease (Lean & Pajonk 2003).

As our environment has grown increasingly obesogenic and more people are given more drugs it is now important to make good data on obesogenicity as a side effect and on effective means to combat it. Obesogenic drugs are used by GP's and also by secondary care specialists. All should take responsibility for managing this side effect within their practice.

RQ3 Are formal protocols to routinely identify and manage overweight/obese patients in place in secondary care clinics?

RQ4 Is height and weight routinely measured in secondary care clinics?

RQ5 What steps are taken to manage patients who are identified as overweight or obese?

This thesis has also highlighted that little is being done in secondary care settings, where the treatment of many disorders associated with obesity is coordinated, to identify and initiate treatment for those who are overweight or obese. The findings concur with previous research (Cleator *et al.*, 2002) and suggest that little has changed since this earlier research.

Although there was a willingness amongst some clinicians to contribute to the identification and management of obesity greater training and resources are required to facilitate this. In the majority of cases patients who were identified as overweight or obese were referred to a dietitian or back to their own GP. In many clinics height and weight were not routinely measured thus the opportunity to identify those who were overweight or obese was missed. Effective tackling of the current "obesity epidemic" will require the involvement of all sectors of the NHS and there should be an integrated approach between primary and secondary care.

A recent Medline literature search found only one publication reporting on the management of overweight patients in a clinic setting (Osland *et al.*, 2007). Weight management was promoted as an important aspect of care for patients attending a liver

management clinic and researchers' reported that providing an intervention for overweight patients in a clinical outpatient setting was a feasible treatment option for weight management.

The results of this survey suggest that weight management should be an integral part of the management and treatment of all chronic non-communicable diseases as it can impact positively on treatment and outcomes.

RQ6 Does a weight reduction diet, that regularly includes lean red meat, maintain iron status in pre-menopausal women?

RQ7 Does a weight reduction diet, which excludes lean red meat, maintain iron status in pre-menopausal women?

RQ8 Does the effects on iron status differ between treatments?

The final study carried out as part of this thesis has shown that improvements in iron status can be achieved during weight loss using eating plans that either include or exclude red meat.

The data however do suggest that a diet including red meat may confer greater benefits on iron status, however as the study was underpowered definitive conclusions are not possible. Earlier research has shown that a meat rich diet was better than supplementation at preserving iron status in premenopausal women participating in an exercise programme (Lye *et al.*, 1992). Other research that compared the effect of iron supplementation and an iron rich diet, showed that while the improvements in serum ferritin achieved with diet were smaller than with supplementation, serum ferritin continued to improve in the diet group beyond the intervention period (Patterson *et al.*, 2001).

The inclusion of red meat provides a more varied diet, a good source of iron and can be part of a healthy balanced diet on which any weight reducing diet should be based. Compliance is a key issue in weight management. Attrition and weight regain in the present study were low and the provision of a varied diet is likely to have been a

contributory factor. It is important that any dietary approach for weight loss facilitates weight loss in a way that does not contribute to the development of nutritional deficiencies. However a larger study over a longer period is required to provide data to support definitive advice.

6.3 Future Research Topics

The possible future research generated by this thesis:

- Can effective interventions be developed to address weight gain in patients who are prescribed drugs associated with weight gain, in both primary and secondary care?
- What resources and training do secondary care clinic staff require to identify those who are overweight or obese, and then initiate treatment within medical specialties?
- What advice and treatment are pre-menopausal women who are identified as iron deficient or with iron deficiency anaemia routinely given?
- Do all weight loss programmes (commercial, self help) advocate a healthy nutritionally balance diet?

6.4 Research Skills developed within this thesis

- Questionnaire development
- Critical appraisal of research literature
- Systematic review methodology
- Critique of evaluation tools
- Co-writing of grant applications
- Completion of ethics applications and attendance at ethics committee meeting
- Redesigning intervention materials
- Intervention implementation and study management
- Preparation of manuscripts and submission for publication
- Preparation and delivery of presentations at International conferences

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APPENDICES

Appendix 1

Obesity/weight management audit

Specialist Area.....

1) Is there a formal protocol in place within your specialist area for overweight/obese patients to receive management?

Yes (If yes please go to question 3)

If you have documentation of your obesity/weight management protocol please enclose a copy with your completed questionnaire. Thank you

No (If no please continue)

2) If at present no protocol is in place within your specialty to address overweight/obesity management can you indicate the possible reasons for this.

Obesity/weight management not a priority for health care in general

Obesity/weight management not important to this specialist area

Expertise not available to treat obesity/overweight within this specialist area

Personnel skilled in weight management inaccessible

Weight management best undertaken by dedicated secondary care specialist service

Weight management should be undertaken by a GP specialist service

Other (please specify)

3a) Are patients' height and weight routinely measured on attendance at your clinic?

Yes

No

3b) If yes who takes these measurements

Doctor

Nurse

Nursing assistant/auxiliary

4) If you consider a patient to be overweight/obese how do you manage this

a) Referral to hospital dietitian for your area

Do they follow the patient up

Yes

No

b) Referral to clinical nurse specialist for your area

Do they follow the patient up

Yes

No

c) Referral to obesity specialist physician

d) Referral back to GP for weight management

e) Referral to commercial slimming organisation

f) No action

g) Other referral *Please specify who/where*

5) Within your specialist area do you currently give advice for reasons other than obesity

Yes *(if yes please tick those appropriate below)*

No

Diet

Activity

Lifestyle

6a) Within your specialist area does obesity affect the outcome or progress of treatment

Yes

No

6b) If yes in what way? (*please state*)

7) Are you comfortable about recommending treatment with anti-obesity drugs that have been recommended by NICE to obese patients within your specialty

Yes

No

If not please state your reasons

8) Two possible models of care for obesity/ weight management may exist or be preferred for development.

Model A: Identify treat and manage obesity within each medical sub-specialty, supported by trained multidisciplinary team

Model B: Identify and refer to specialist obesity clinic

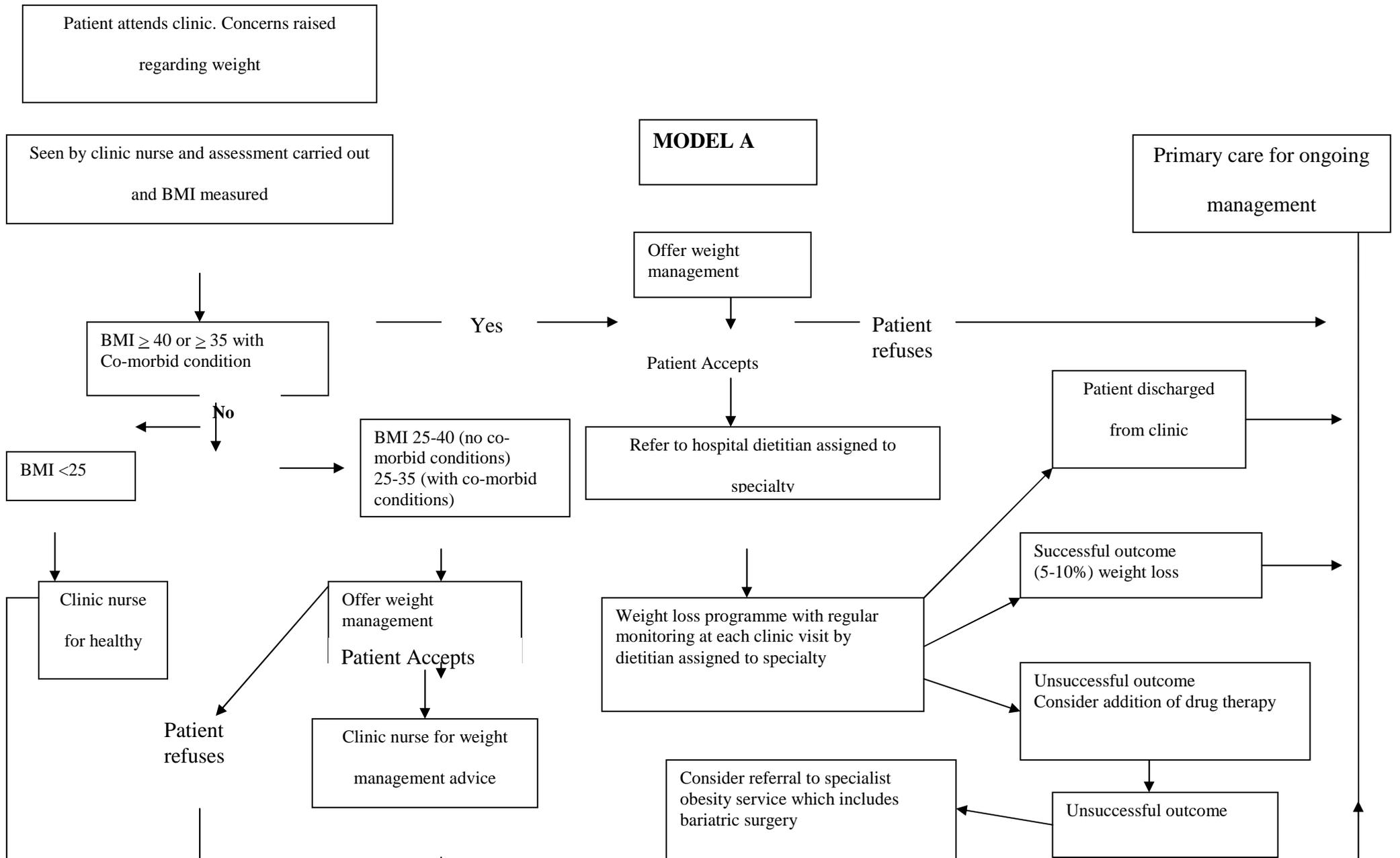
Please see over for flow diagram of each model

Please indicate which model you would prefer to see implemented

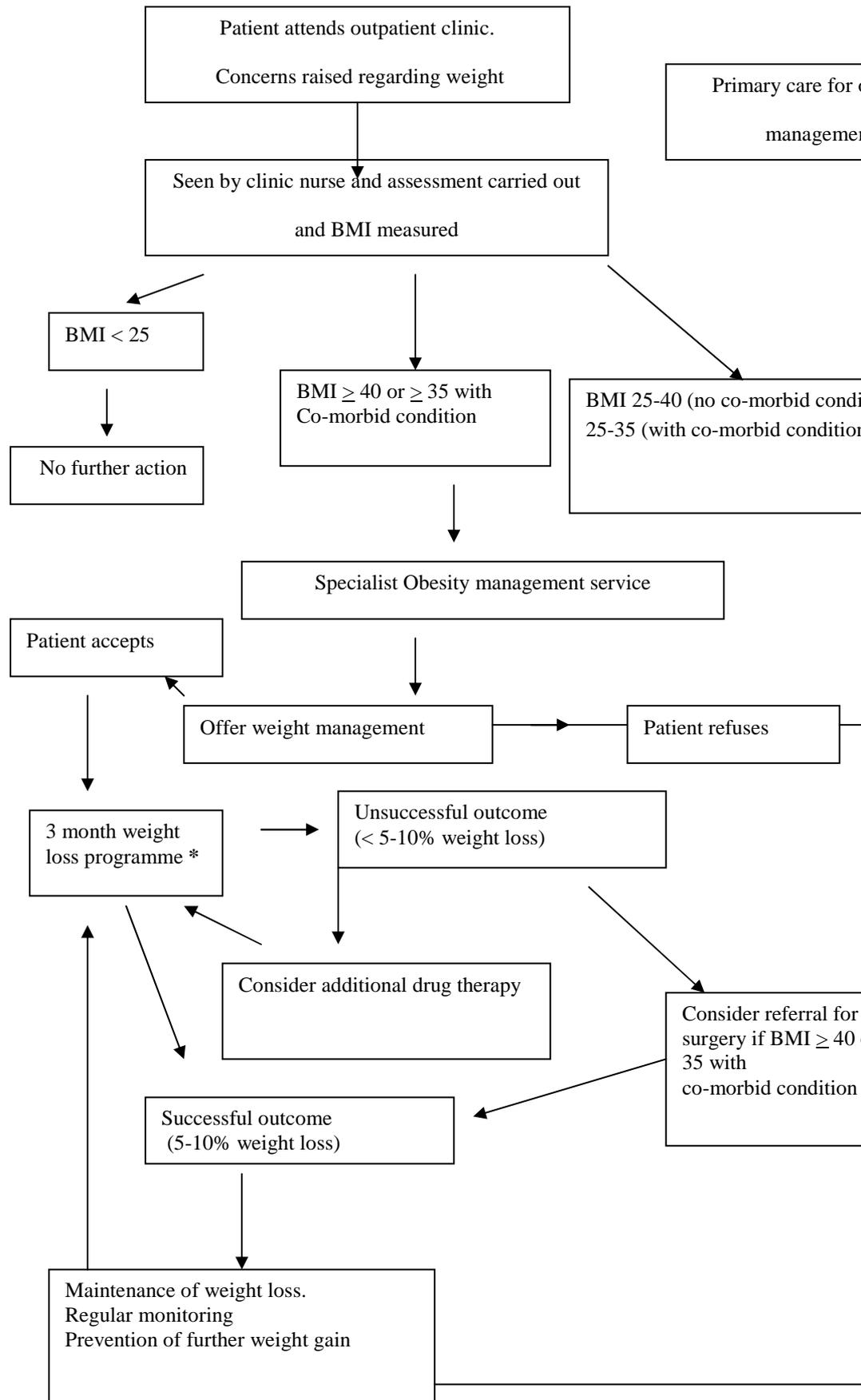
Model A

Model B

We would welcome any additional comments you may have on either Model or any other point raised in this questionnaire



Model B



* Specialist obesity dietitian will deliver programme

Appendix 2

RECRUITMENT POSTER

Is iron status in dieting pre-menopausal women affected by red meat consumption?

Are you interested in losing weight? We at the Department of Human Nutrition at the University of Glasgow are carrying out a study and would like to invite you to take part.

What's it all about?

Women often have low iron levels and many may be overweight. When trying to lose weight many women often exclude red meat from their diet as they think it is "high in fat". We would like to find out what effect a diet for weight loss that excludes red meat has on iron levels compared to one that includes red meat.

Who can take part?

Women, who have not reached the menopause, are overweight, would like to lose weight and have a low level of iron.

How will I know if I can take part?

Two things will be checked:

1. height and weight to find out if you are overweight.
2. iron levels in a sample of your blood.

If your results show that you are **overweight** and your **iron levels are low** you would be able to take part.

What next?

If you are eligible to take part in this study, you will be asked to follow one of two diets, one that allows you to eat red meat or one that doesn't. The diet you will be asked to follow will be decided by chance using a computer programme. The study will last for 24 weeks in total, for the first 12 weeks you will be asked to lose weight and for the second 12 weeks to maintain the weight you have lost. During the whole 24 weeks you will be asked to attend an appointment with the study researcher every 2 weeks. Your weight will be measured and your progress discussed on each occasion. All appointments will take place at your place of work.

What's in it for me?

You will be given expert dietary advice to help you improve your diet. Losing weight has many health benefits.

Interested in taking part: what next?

If you are interested in taking part you can call us on 07814 066 483 Monday to Friday between 9am and 5pm and we can discuss the study in more detail without any obligation on your part. We will also be in.....on..... Your decision on whether to take part or not, will not affect your employee/employer relationship in any way.

Look forward to hearing from/meeting you

Wilma Leslie

Catherine Hankey

Appendix 3

North Glasgow University Hospitals
Division



West Glasgow Ethics Committee
Western Infirmary
Dumbarton Road
Glasgow G11 6NT

Tel: 0141 211 6238

Email:

andrea.torrie@northglasgow.scot.nhs.uk

09 September 2004

Ms Wilma Leslie
Research Nurse
University of Glasgow
Glasgow Royal Infirmary
10 Alexandra Parade
Glasgow
G31 2ER

Dear Ms Leslie,

A handwritten signature in cursive script that reads 'Wilma'.

Full title of study: Is iron status in dieting pre-menopausal women affected by red meat consumption
REC reference number: 04/S0703/54
Protocol number: RDF 014

The Research Ethics Committee reviewed the above application at the meeting held on 07 September 2004.

Ethical opinion

The Committee thanked the investigators for attending to meeting to discuss and explain their study.

The Committee discussed the above study at length and had various comments most of which was able to be clarified by your attendance at the meeting.

Study Design:

- a) The Committee were concerned that there might be a conflict of interest between the supermarket i.e Sainsbury's and the Meat and Livestock Committee providing the funding for the study.
- b) The Committee wished the investigators to draw up and issue to participants an exercise diary.
- c) The Committee wished people with significant anaemia (less than 10) to be excluded from the study.
- d) The Committee wished people with a low ferritin level (less than 10) to be excluded.

The Committee wished the University to ensure that any negative results recorded will be published. The Meat and Livestock Commission should have no influence on the results which are published.

- f) The Committee did not wish the initial contact to be via letter in employees pay packets. Posters should be displayed in the canteen/tea bar inviting staff to apply to enter the study.
- g) The Committee were of the opinion that results should be fed-back via the Occupational Health Department at Sainsbury's and not the site manager.
- h) The Committee also suggested that the investigators should take into account gynaecological history i.e. whether the participants are on any hormonal treatments, tranexamic acid or mefenamic acid. Also they should take into account any significant menstrual blood loss.
- i) The Committee do not feel that Maureen Strong is the right person to supervise the study - this should be someone from the University.

The Information Sheet and poster should be amended as under:

The title on the Information Sheet and poster should be the same as the study title.

- a) The volume of blood taken should be stated in layman's terms i.e. a teaspoonful etc etc.
- b) Mention should be made of the time taken to participate in the study and whether this is Sainsbury's time or the participant's time.
- c) Mention should be made that the results may identify a significant illness which may require future medical management.
- d) Mention should be made that the participant's GP will be informed. Anyone not wishing GP to be informed should be excluded from the study.
- e) The Information Sheet and poster should have a sentence added - "Your involvement/or not in this research will not affect your employee/employer relationship".
- f) Penultimate sentence on poster should read "Feel free to come along etc etc".
- g) Information Sheet - 1st sentence should read "you are etc etc in a research study that is being funded by the Meat and Livestock Commission. This study which has been funded etc etc. (3rd para moved to here).

The above amendments should come back to the secretary for filing.

The members of the Committee present gave a favourable ethical opinion to the above research on the basis described in the application form, protocol and supporting documentation.

The favourable opinion applies to the research sites listed on the attached sheet. Confirmation of approval for other sites listed in the application will be issued as soon as local assessors have confirmed that they have no objection.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The documents reviewed and approved at the meeting were:

Document Type: Application

Version:

Dated: 10/08/2004

Date Received: 16/08/2004

Document Type: Investigator CV

Version:
Dated: 16/08/2004
Date Received: 16/08/2004

Document Type: Protocol
Version: RDF 014
Dated: 16/08/2004
Date Received: 16/08/2004

Document Type: Covering Letter
Version:
Dated: 16/08/2004
Date Received: 16/08/2004

Document Type: Copy of Questionnaire
Version:
Dated: 16/08/2004
Date Received: 16/08/2004

Document Type: Letters of Invitation to Participants
Version:
Dated: 16/08/2004
Date Received: 16/08/2004

Document Type: GP/Consultant Information Sheets
Version:
Dated: 16/08/2004
Date Received: 16/08/2004

Document Type: Participant Information Sheet
Version:
Dated: 16/08/2004
Date Received: 16/08/2004

Document Type: Participant Consent Form
Version:
Dated: 16/08/2004
Date Received: 16/08/2004

Management approval

If you are the Principal Investigator for the lead site: You should obtain final management approval from your host organisation before commencing this research.

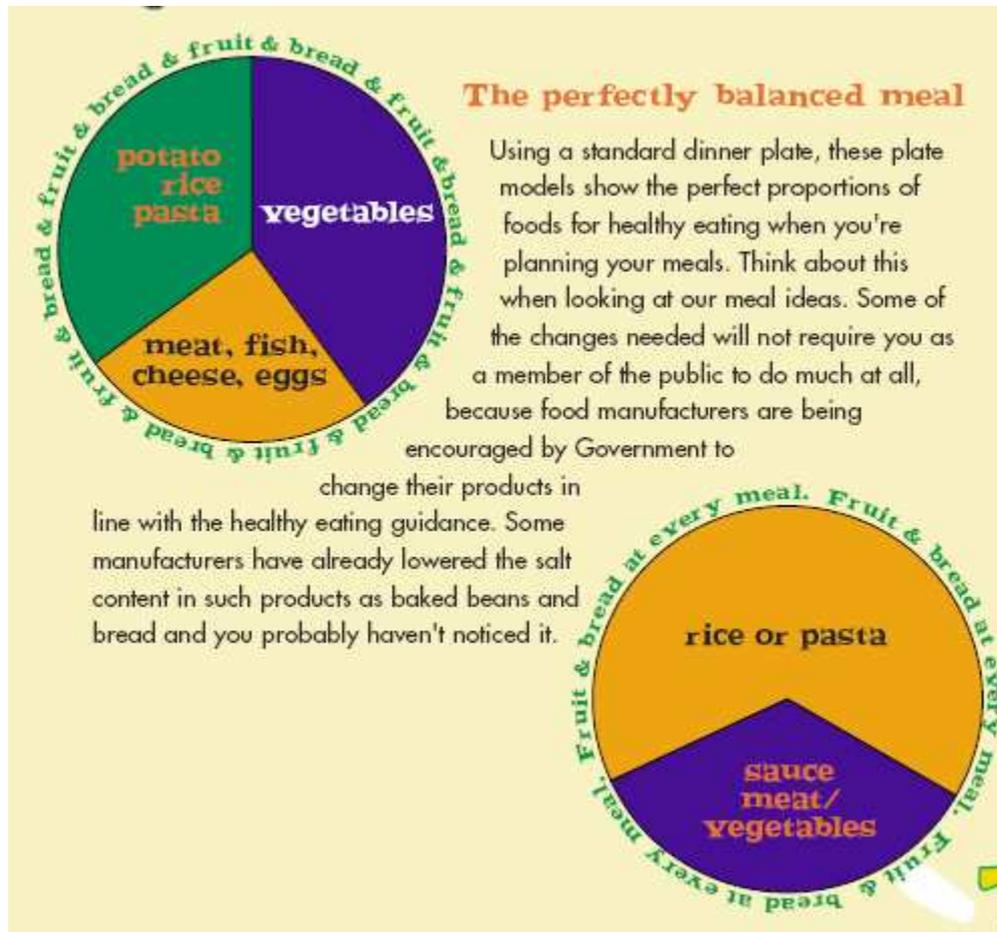
The study should not commence at any other site until the local Principal Investigator has obtained final management approval from the relevant host organisation.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant host organisation before commencing any research procedures. Where a substantive contract is not held with the host organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Membership of the Committee

Appendix 4

Plate Models



Appendix 5

The Healthy plan 13

Daily allowances

1/2 pint semi skimmed milk. (250 ml)

(100 ml of milk can be taken as a diet or natural yoghurt)

7 x carbohydrate exchange

2 x protein exchange

2 x fruit exchange

1 x wine glass fruit juice (125 ml)

Low fat spread:(40g or less fat per 100g)

20g or 2 scrapes

Suggested meal plan

Breakfast

1 x glass of fresh fruit juice

2 x carbohydrate exchange

Spread jam or marmalade

Tea / coffee

Mid-Morning

Tea / Coffee or low calorie drink

Lunch

2 x carbohydrate exchange

1 x protein exchange

Salad / vegetable

1 x fruit exchange

Tea / Coffee or low calorie drink

Mid afternoon

Tea / Coffee or low calorie drink

Evening meal

1 x protein exchange

2 x carbohydrate exchange

Salad / vegetable

1 x fruit exchange

Supper

1 x carbohydrate exchange

Appendix 6 Dietary Targets monitor

(Lean MEJ, Anderson AS, Morrison C, Currall J, (2003) Evaluation of a Dietary Targets Monitor. *European Journal of Clinical Nutrition* **57**, 667-673)

DATE _____

STUDY NUMBER | _____

1. What kind of bread do you usually eat

- white
- brown, granary, wheatmeal
- wholemeal
- other kind (please specify)
- no usual type
- do not know
- do not eat bread

2. What do you usually spread on bread?

- butter
- hard/block margarine
- soft margarine
- reduced fat spread
- low fat spread
- no usual type
- do not know
- do not spread fat on bread

3. How much do you usually eat in a day?

- slices of bread/rolls
- biscuits (including chocolate biscuits)
- cakes, scones, sweet pies and pastries

less than 1	1	2-3	4-5	6 or more

4. What kind of milk do you usually use for drinks in tea or coffee and on cereals etc?

- whole milk
- semi-skimmed
- skimmed
- other kind (please specify)
- no usual type
- do not know
- do not drink milk

5. Do you usually take sugar in:

- (a) tea
- (b) coffee

YES	NO

Appendix 7

1300 kcal Eating Plan

Daily allowances

7 x carbohydrate exchange

2 x protein exchange

3 x fruit exchange

Meal	Portion size	Iron Content (mg)	Vitamin C Content (mg)
<i>Breakfast</i>			
One slice wholemeal toast	31g	0.9	
Special K	84g	19.5	
Fresh Orange juice	125ml	0.5	48.7
<i>Lunch</i>			
2 slices wholemeal bread	52g	1.2	
Chicken breast	75g	0.5	
Banana	80g	0.2	8.8
<i>Evening Meal</i>			
Boiled potatoes	240g	0.9	13.0
Stewed mince OR	75g	2.0	
Fried haddock in breadcrumbs	125g	1.0	
Broccoli (boiled)	80g	1.7	35.2
Carrots (boiled)	80g	0.3	1.6
Apple	80g	0.08	4.8
<i>Supper</i>			
One slice wholemeal toast	31g	0.9	
Total		28.6 (meat) 27.6 (no meat)	112.1

* Iron and Vit C content calculated using Food Composition Tables, McCance & Widdowson 6th Summary Edition 2008

Appendix 8

Q J Med 2007; **100**:395–404
doi:10.1093/qjmed/hcm044

Review

QJM

Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review

W.S. LESLIE, C.R. HANKEY and M.E.J. LEAN

From Human Nutrition, Division of Developmental Medicine, University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK

Summary

Several drugs, or categories of drugs, listed by the WHO and other writers and used in the treatment of chronic disease, are consistently associated with weight gain as a side effect and considered 'obesogenic'. The extent to which they may contribute to the multifactorial process behind obesity is not well documented. We systematically reviewed papers from Medline 1966–2004, Embase 1980–2004, PsycINFO 1967–2004, and Cochrane Register of Controlled Trials, to determine the effect on body weight of some drugs that are believed to favour weight gain. We included randomized controlled studies of adult participants (>18 years) prescribed a drug considered obesogenic, that compared the 'obesogenic' drug with placebo, an alternative drug or other treatment, and that had a duration of at least 3 months: 43 studies totalling

25 663 subjects met these criteria. The main objective of the majority of studies was to compare the efficacy and safety of drug therapy, with weight change recorded under safety outcomes; weight change was a primary outcome measure in only six studies. There was evidence of weight gain for all drugs included, up to 10 kg at 52 weeks. Differences in dosage, patient population, duration of treatment and dietary advice make generalization of the results difficult. Data on body weight are often not recorded in published clinical trials or is reported in insufficient detail. This side-effect has potentially serious consequences, and should be mentioned to patients. Weight management measures should be routinely considered when prescribing drugs known to promote weight gain. Future clinical trials should always document weight changes.

Introduction

Obesity continues to increase in prevalence.^{1–3} In the UK, around half of women and two-thirds of men are overweight or obese.^{4,5} Recent Scottish data show that the figure for women has risen to 60%.⁶ In addition to being a major health problem in its own right, obesity is associated with a range of serious symptoms and co-morbid conditions. The estimated cost to the UK Health Service of obesity and related conditions at present is immense.^{5,7} If the rise in obesity continues, it is thought that by the

year 2010 one third of all adults in the UK will be obese,⁸ and the costs to health care services will rise to an estimated £3.6 billion.⁵

Obesity is a consequence of energy imbalance, when energy intake exceeds energy expenditure over a prolonged period of time. Social and environmental forces have a powerful influence over energy intake and expenditure, and individuals vary in their susceptibility to these influences due to genetic and biological factors. It is the interaction of

Address correspondence to W.S. Leslie, Human Nutrition, Division of Developmental Medicine, University of Glasgow, Queen Elizabeth Building, Glasgow Royal Infirmary, Glasgow G31 2ER. email: w.s.leslie@clinmed.gla.ac.uk

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Table 1 Drugs known to favour weight gain

Drug	Main use
Insulin, sulphonylureas, thiazolidiniones	Diabetes
Beta-blockers	Hypertension
Corticosteroids	Inflammatory disease
Cyproheptadine	Allergy, hay fever
Antipsychotics	Psychosis
Sodium valproate	Epilepsy
Tricyclic antidepressants	Depression
Lithium	Bipolar disorder

From references 3, 9, 10, 11, 12.

all these elements that gives rise to obesity.³ Many prescription drugs in current use are associated with weight changes. For some (e.g. certain serotonin reuptake inhibitors, oral contraceptives), the evidence of an effect on body weight is less consistent,⁹ while others are consistently associated with weight gain, and are considered obesogenic^{3,10-12} (Table 1). This effect can arise as a consequence of differing mechanisms, such as increased appetite (corticosteroids) or reduced metabolic rate (beta-adrenoceptor blockers).¹¹ For some drugs, weight loss may have occurred as a result of the underlying disease and recovery on effective treatment will include weight regain, which would not be considered an adverse effect. However, in many cases, weight gain is an unwanted side-effect. These drugs are used in the management of chronic disease and therefore prescribed on a long-term basis. In previous research, 9% of adults attributed weight gain to drugs they were prescribed.¹³

The development of obesity is a long-term multifactorial process in which obesogenic drugs play a contributory role. This review quantifies the adverse effects on body weight of those drugs that are consistently reported as obesogenic, and that are used in the treatment of chronic disease (Table 1).

Methods

We electronically searched Medline 1966–2004, Embase 1980–2004, PsycINFO 1967–2004, and the Cochrane Register of Controlled Trials. The drug name or drug category was the primary key word for each search. This was mapped to relevant subheadings. The second keyword search used the terms 'weight adj2 gain' or 'weight adj2 change'. Primary and secondary searches were then combined and limited to human, English language, adults, clinical trial, randomized controlled trial or controlled clinical trial. Reference lists of all relevant papers

were checked. We did not hand-search journals or search the 'grey' literature as part of this review.

Selection of studies

Articles were selected on the basis of title and abstract. Studies were included according to the following eligibility criteria: only randomized controlled studies; adult participants (>18 years) prescribed a drug considered obesogenic; duration ≥ 3 months; comparison of the 'obesogenic' drug with placebo, an alternative drug or other treatment. Outcome measures had to include measured weight change, reported quantitatively. Studies that primarily investigated the use/effect of a combination of 'obesogenic' drugs were excluded, as were studies in which body weight was self-reported. Studies where the drug was used to treat diseases characterized by weight loss (e.g. type 1 diabetes) were also excluded.

Quality assessment

Two reviewers checked independently that the studies identified by the search strategy met the inclusion criteria, and assessed the methodological quality of the included studies. Quality assessment focussed on the adequacy of the randomization procedure.¹⁴ As the identified studies involved different populations, drugs and dosages, no quantitative meta-analyses were done.

Results

A total of 628 titles and abstracts were reviewed, and 139 publications were retrieved and reviewed in greater detail. From these, 43 studies (total 25 663 subjects) were identified that met our inclusion criteria. The main reasons for exclusion were: study duration <12 weeks; non-randomized study design; weight gain not reported or not quantified (Figure 1).

Valproate

All four studies compared valproate with an alternative drug; no placebo-controlled studies were identified. Comparison was made with olanzapine in the treatment of bipolar disorder¹⁵ and acute mania.¹⁶ The objective of both these studies was to compare the drugs in terms of efficacy and safety. Biton *et al.*¹⁷ compared valproate with lamotrigine in patients with epilepsy. The aim of the fourth study¹⁸ was to determine the efficacy and safety of topiramate, in comparison with cabamazepine and valproate monotherapy, in the initial treatment of newly diagnosed epilepsy.

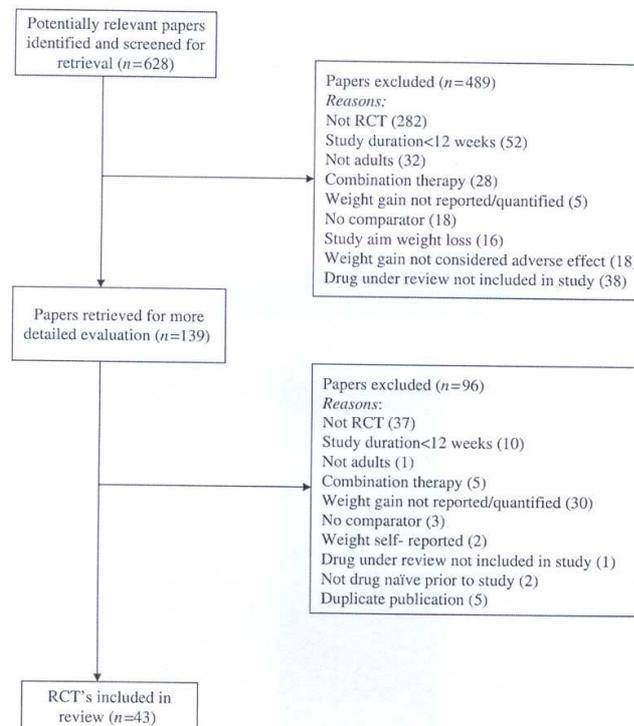


Figure 1. Flowchart of progress of papers through the review.

Weight change was the primary outcome measure in only one study,¹⁷ and a secondary measure to assess safety in the remaining studies. The mean dosage of valproate differed in each study (Table 2).

Lithium

Only one study fulfilled the inclusion criteria and compared lithium with carbamazepine as a prophylactic agent in bipolar disorder.¹⁹ The main outcome measure was relapse, with weight gain recorded as an assessment of side-effects. The initial dose of lithium was 400 mg twice daily.

Atypical antipsychotics

In three studies, olanzapine was compared with placebo in the treatment of alcohol dependence disorder,²⁰ and borderline personality disorder.^{20,21} Ziprasidone was compared with placebo in the treatment of schizophrenia.²³ In the remaining studies, comparisons were made between an atypical antipsychotic and an alternative drug: clozapine, olanzapine, and risperidone vs. haloperidol,²⁴ olanzapine vs. sodium valproate,^{15,16}

olanzapine vs. haloperidol,^{25,26} risperidone vs. amisulpride,²⁷ clozapine vs. chlorpromazine,²⁸ olanzapine vs. aripiprazole²⁹ and olanzapine vs. amisulpride.³⁰

Only two studies^{24,29} specifically examined weight change as a primary outcome; in the remainder of the studies, clinical response was the primary outcome with weight change recorded as a means of assessing safety.

Corticosteroids

Only one randomized controlled trial was identified,³¹ comparing prednisone with radiotherapy in the treatment of Graves' ophthalmopathy. The objective of the study was to compare the efficacy and tolerability of the treatments: clinical response was the primary outcome measure, with weight change recorded as a side-effect.

Insulin

The studies included were restricted to the treatment of type 2 diabetes. In all studies, insulin therapy alone was compared with either oral agents^{32–34} or with

Table 2 Drugs and their effect on body weight

Drug	Reference	Condition	Follow-up (weeks)	n	Dose	Weight change (kg)
Valproate	Zajacka 2002 ^{15,#}	Bipolar disorder	12	120	2115 mg/day*	+2.5**
	Biton 2001 ¹⁷	Epilepsy	32	141	1822 mg/day*	+5.8 (SD 4.2)
	Tohen 2003 ¹⁶	Bipolar disorder	47	251	1500 mg/day*	+1.2(SE 1.2)
	Privitera 2004 ¹⁸	Epilepsy	26	621	1250 mg/day	+2.0**
Lithium	Coxhead 1992 ¹⁹	Bipolar disorder	52	32	≥400 mg/day	+4.0**
	Czobor 2002 ²⁴	Schizo-affective disorder	14	151	200–800 mg/day	+4.2 (SD 4.7)
Clozapine	Lieberman 2003 ²⁸	Schizophrenia	52	160	≤400 mg/day	+9.9**
	Zajacka 2002 ^{15,#}	Bipolar disorder	12	120	14.7 mg/day*	+3.9**
Olanzapine	Lieberman 2003 ²⁶	Psychosis	12	263	9.1 mg/day*	+7.1 (SD 6.1)
	Czobor 2002 ^{24,#}	Schizo-affective disorder	14	151	30.4 mg/day*	+5.4 (SD 4.6)
	Zanerini 2001 ²²	Borderline personality disorder	24	28	5.3 mg/day*	+2.8 (SD 5.7)
	Tohen 2003 ^{16,#}	Acute mania	47	251	16.2 mg/day*	+2.8**
Olanzapine	Tran 1999 ²⁵	Schizo-affective disorder	51	110	11.5 mg/day*	+5.0 (SD 7.3)
	Guardia 2004 ²⁰	Alcohol dependence	12	60	5–15 mg/day	+4.3**
	Bogenschutz 2004 ²¹	Borderline personality disorder	12	40	2.5–20 mg/day	+3.7 (SD 3.4)
	McQuade 2004 ²⁹	Schizophrenia	26	317	10–20 mg/day	+4.2**
Risperidone	Mortimer 2004 ³⁰	Schizophrenia	26	377	5–20 mg/day	+3.9 (SD 5.3)
	Czobor 2002 ^{24,#}	Schizo-affective disorder	14	151	7.9 mg/day*	+2.3 (SD 2.8)
Ziprasidone	Sechter 2002 ²⁷	Schizophrenia	24	309	4–10 mg/day	+2.1**
	Arato 2002 ²³	Schizophrenia	52	294	40 mg/day	–2.7**
					80 mg/day	–3.2**
Prednisone	Prummel 1993 ³¹	Graves ophthalmopathy	24	56	160 mg/day	–2.9**
					Decreasing	+2.0**
Insulin	Yki-Jarvinen 1992 ³⁶	Type 2 diabetes	12	153	2 injections	+1.8 (SD 0.5)
					Multiple injections	+2.9 (SD 0.5)
					2 injections	+5.2(SD 4.1)
					1 injection	+6.6**
					2 injections	+3.9**
Glipizide	UKPDS 1998 ^{34,#}	Type 2 diabetes	10 yrs	3867	1–2 injections	~+6.5**
					5–60 mg/day	–0.3 (SD 0.2)
	Simonson 1997 ³⁸	Type 2 diabetes	16	143	5–20 mg/day	–0.1 (SD 0.1)
					5–30 mg/day	+2.6**
	Campbell 1994 ⁴²	Type 2 diabetes	52	48	0.5–12 mg/day	+3.6**
					1.25–20 mg/day	+2.3**
	Marbury 1999 ⁴³	Type 2 diabetes	52	576	2.5–10 mg/day	+3.8**
					1–4 mg/day	+2.3**
	Johnstone 1998 ⁴¹	Type 2 diabetes	52	411	2–8 mg/day	+0.8**
					2.5–10 mg/day	+2.3**
Nathan 1988 ^{32,#}	Type 2 diabetes	36	31	1–4 mg/day	+2.3**	
				2–8 mg/day	+0.8**	
Bautista 2003 ³⁹	Type 2 diabetes	14	70	2.5–20 mg/day	~+4.0**	
				3.5 mg/qid	+1.4**	
Tan 2004 ^{48,#}	Type 2 diabetes	52	244	100–500 mg/day	~+5.0**	
				400 mg/day	+0.06 (SD 1.6)	
UKPDS 1998 ^{34,#}	Type 2 diabetes	10 yrs	3867	0.05 mg/day	–0.95**	
				0.25 mg/day	–0.54**	
Segal 1997 ⁴⁰	Type 2 diabetes	24	201	1.0 mg/day	+0.18**	
				2.0 mg/day	+0.36**	
Chlorpropamide	UKPDS 1998 ^{34,#}	Type 2 diabetes	10 yrs	3867	400 mg/day	+0.06 (SD 1.6)
					400 mg/day	+0.06 (SD 1.6)
Troglitazone	Iwamoto 1996 ⁴⁵	Type 2 diabetes	12	284	0.05 mg/day	–0.95**
					0.25 mg/day	–0.54**
Rosiglitazone	Patel 1999 ⁴⁴	Type 2 diabetes	12	380	1.0 mg/day	+0.18**
					2.0 mg/day	+0.36**
					2.0 mg/day	+0.36**

(Continued)

Table 2 Continued.

Drug	Reference	Condition	Follow up (weeks)	<i>n</i>	Dose	Weight change (kg)
Pioglitazone	Wallace 2004 ⁴⁶	Type 2 diabetes	12	30	45 mg/day	+0.70 (SE 0.6)
	Tan 2004 ^{48,#}	Type 2 diabetes	52	244	15–45 mg/day	+1.5**
	Schernthaner 2004 ⁴⁷	Type 2 diabetes	52	1199	≤45 mg/tid	+1.9**
Nortriptyline	Weber 2000 ⁴⁹	Depression	12	32	NA	+3.7 (SD 2.3)
Doxepin	Feighner 1986 ⁵⁰	Depression	13	147	100–225 mg/day	+2.7**
Amitriptyline	Montgomery 1998 ⁵¹	Depression	104	217	max 280 mg/day	+1.7 (SD 4.1)
Atenolol	Houston 1991 ⁵³	Hypertension	13	49	56 mg/day*	+1.0**
Atenolol or metoprolol	Wilhelmsen 1987 ⁵⁷	Hypertension	45 months	6569	100/200 mg/day	+1.1**
Metoprolol	Wikstrand 1988 ⁵⁶	Hypertension	208	3234	174 mg/day*	+1.5**
	Foss 1990 ⁵⁰	Hypertension	26	114	50–200 mg/day	+0.5 (females)** +0.7 (males)**
Propranolol	Rossner 1990 ⁵⁴	Post myocardial infarction	52	3837	Not stated	+2.3**
	Berglund 1986 ⁵⁵	Hypertension	10 yrs	106	80 mg/bd*	–0.6**

*Mean dose. **SD or SE not reported. #Duplicate reporting of studies as a result of the comparator in each study.

insulin plus oral agents.^{35–37} The dosage of insulin varied in each study, and was calculated according to the participant's body weight, subsequently adjusted according to blood glucose results.

Sulphonylureas

Treatment with a sulphonylurea was compared with placebo alone in two studies,^{38,39} with another oral hypoglycaemic agent and placebo in two studies,^{40,41} with insulin in two studies,^{32,34} and with an alternative oral hypoglycaemic agent in three studies.^{42,43,48} Weight change was a primary outcome measure in only one study.⁴² In the UKPDS study, the main objective was to determine the risk of micro or macro-vascular complications, with weight change recorded under adverse events. The objective of the remaining studies was to determine efficacy, safety and tolerability, with clinical response as the primary outcome measure and weight change recorded under safety outcomes.

Thiazolidinediones

Three studies compared a thiazolidinedione with placebo in type 2 diabetic patients. Patel *et al.*⁴⁴ assessed the metabolic effects of four doses of rosiglitazone, Iwamoto *et al.*⁴⁵ investigated the efficacy and safety of troglitazone and Wallace *et al.*⁴⁶ examined the effect of pioglitazone on beta cell function and insulin sensitivity. The metabolic effects of pioglitazone were compared with

metformin in one study,⁴⁷ and in the final study pioglitazone was compared with glimepiride with regard to changes in glycaemic control and insulin sensitivity.⁴⁸ In all studies, weight change was a secondary outcome.

Tricyclic antidepressants

All three studies compared the efficacy and tolerability of a tricyclic antidepressant with an alternative anti-depressant: paroxetine in comparison with nortriptyline,⁴⁹ bupropion compared with doxepin,⁵⁰ and mirtazapine with amitriptyline and placebo.⁵¹ Weight change was the primary outcome measure in one study,⁴⁹ and assessed as an adverse event in the other two. The dosage of tricyclic antidepressant was not reported in one study,⁴⁹ and differed in the other two.

Beta-adrenergic blocking agents

Two studies compared the effect on lipid profiles between a chosen beta-blocker and an alternative anti-hypertensive agent: captopril vs. metoprolol⁵² and nifedipine vs. atenolol.⁵³ The effect of long-term treatment with propranolol on body weight study was the main outcome in one study.⁵⁴ Two studies compared treatment with a beta-blocker with bendroflumethiazide: one investigated the metabolic effects,⁵⁵ the other compared the effects on mortality.⁵⁶ Wilhelmsen *et al.*⁵⁷ compared beta-blocker treatment with diuretic treatment to determine differences in the incidence of non-fatal

myocardial infarction, coronary heart disease mortality and total mortality.

Cyproheptadine

No studies were identified that fulfilled the inclusion criteria.

Methodological quality of included studies

All studies included in this review were described as randomized, but in the majority (72%) the methods of randomization and concealment were not described. In one study,³⁵ the method of randomization (consecutive and alternate) was inadequate.¹⁴ In 11 studies the method of randomization was clearly described and considered adequate. Inclusion and exclusion criteria were clearly described in all studies. Intention-to-treat analysis was used in 51% of studies.

Weight change

In the majority of studies, weight change was not a primary outcome measure, but was measured and recorded under safety outcomes; weight change was a primary outcome measure in only six studies.^{17,24,29,42,49,54} The effects on body weight differed greatly amongst the different categories of drugs. In the majority of studies, weight gain was the result of treatment, with some of the greatest weight gains seen in subjects prescribed anti-psychotic medications. However, weight loss was observed in some studies (Table 2).

Six studies investigated whether weight gain was dose-related. Results varied, with three studies reporting no relationship between drug dosage and weight gain.^{17,23,24} Some correlation was observed between dosage of insulin and weight gain.^{35,36} One study⁴⁴ suggested that a clinically significant increase in body weight might be observed at higher doses of rosiglitazone.

Discussion

Weight change occurs over time and against a background of progressive weight gain in the 'normal' population. There is no ideal time to examine the possible obesogenic effects of drugs. It can be assumed that most such drugs will have a most marked effect early in treatment, reaching a plateau effect by 6–12 months (although all healthy subjects are likely to continue to gain weight at around 1 kg/year).^{58,59}

If the underlying disease for which the drug was prescribed has caused weight loss, then recovery on effective treatment will include weight regain.

The primary treatment of type 1 diabetes is an obvious example. This was not considered an obesogenic effect, and such studies were excluded by our own inclusion criteria.

The effect of the drug treatment on body weight was reported in all of the studies in this review, and provides evidence that weight gain is associated with some drugs, and is a major and continual burden on public health. All of the drugs included in this review are used in the treatment of chronic disease. In the UK, it is estimated that around 2.6 million people have been diagnosed with coronary heart disease,⁶⁰ and beta-blockers (unless contraindicated) have a prominent role in its management.^{61–63} Valproate is one of the first-line treatments for epilepsy,⁶⁴ and is also used in the treatment of manic episodes associated with bipolar disorder. In Scotland, around 20 000–40 000 people have active epilepsy, with about 2000–3000 new cases per year.⁶⁴ In England ~380 000 people suffer from the disease (1:130 people).⁶⁵ Bipolar disorder is the third most common mood disorder after major depression and schizophrenia, and affects around 1% of the population.⁶⁶ Around 1.3 million people in the UK suffer from either type 1 or type 2 diabetes.⁶⁰ In the light of these figures, the number of individuals in the population receiving treatment with an obesogenic drug is potentially quite high. In Scotland alone, the number of prescriptions dispensed for beta-blockers and tricyclic antidepressants between 2004 and 2005 exceeded 1 million and 2 million, respectively (Table 3) (Audrey Thompson, personal communication).

It is generally accepted that during adult life, most people will gain weight. The rate at which weight is gained varies, but a 0.5–1 kg gain per year

Table 3 Prescribing by GP practices in Scotland, April 2004–March 2005

Drug class	No. of prescriptions
Beta-blockers (BNF 2.4)	2 936 456
Atypical antipsychotics	275 114
Lithium	81 252
Sodium valproate	193 064
Tricyclic antidepressant	1 134 611
Intermediate and long-acting insulins	352 632
Short-acting insulins	105 207
Suphonylureas	442 833
Pioglitazone	36 898
Rosiglitazone	65 458
Glucocorticoid therapy (BNF 6.3.2)	517 366

is considered average in the general population.^{58,59} In some studies in this review, weight gain in excess of this was observed over a much shorter duration: in particular, those involving anti-psychotic drugs. Olanzapine and clozapine were associated with the greatest weight gains, a finding that concurs with previous reviews in this area.^{67,68} The weight gains with beta-blocker therapy were relatively small, but more marked in those prescribed propranolol. Previous research has also identified propranolol as the beta-blocker most likely to cause weight gain.^{69,70}

In the UK at present, a significant proportion of the population are considered either overweight or obese,^{5,6} and an annual weight gain of 5 kg/year or more is not uncommon. It is therefore likely that prior to treatment with a drug known to favour weight gain, many individuals will already be overweight and struggling to avoid further gain. The additional effect of obesogenic drug therapy may tip the balance to increase BMI towards the obese category, or be sufficient to make co-morbidities clinically apparent. Given the common and long-term use of many of these drugs, it is likely that they play a significant contributory role in the increasing prevalence of obesity.

Non-compliance with any drug therapy is a widespread problem,⁷¹ and around half of patients prescribed long-term medication for the management of chronic diseases do not comply fully with treatment.⁷² Poor compliance with drug therapy may lead to a worsening of the underlying condition and contribute to increased health care costs.⁷³ Non-compliance is reported as an issue with many of the drugs included in this review,⁷³⁻⁷⁶ and the weight gain associated with them may contribute to this. For those prescribed anti-psychotic medication, weight gain is acknowledged as a major cause of non-compliance.⁷⁶ It is unclear whether this known side-effect is routinely discussed with patients prior to prescription but it should be, on medico-legal grounds. The treatment of anti-psychotic-induced weight gain is now considered a treatment priority,⁷⁷ and research on approaches to address this is a growing area.⁷⁷⁻⁸¹ It would seem greatly preferable to discuss the probability of weight gain as a side-effect, and to provide effective advice and support to avoid weight gain. For a number of the drug classes included, weight management should form an essential part of treatment for the underlying disease, e.g. in type 2 diabetes and hypertension, access to dietitians should be routine. For other drugs (notably anti-psychotics) provision of dietary advice is a new consideration.⁸²

Study limitations

The drugs included in the present review were those consistently reported in medical/scientific literature, used in the treatment of chronic disease and believed to affect weight.^{3,9-12} Many other drugs prescribed today may also affect weight. Few studies included in the review examined weight change as a primary outcome, and in many instances the variability of weight change was not reported. Studies that primarily investigated the effect of a combination of 'obesogenic' drugs were excluded, but it was not always possible to be certain that other drugs known to favour weight gain were not also being taken. However, the process of randomization should have ensured that any such confounding effect would have been similar in all groups.

Conclusions

This review provides evidence of the weight gain potential of some common drugs. It is perhaps only now, in light of the present epidemic of obesity, that the negative effect on body weight is a pertinent issue. Body weight and height are routinely recorded in virtually all clinical trials, but seldom reported. The potential of weight gain should be discussed with patients prior to the institution of therapy, both for medico-legal grounds and to ensure that weight maintenance is promoted and adhered to.

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Appendix 9

Weight management: a survey of current practice in secondary care NHS settings in 2004

W. S. Leslie RGN BA MSc,¹ C. R. Hankey SRD BSc MSc PhD,² L. McCombie SRD BSc³ and M. E. J. Lean MA MB BChir MD FRCP FRCPS⁴

¹Researcher, ²Lecturer, ³Dietician, ⁴Professor, Human Nutrition, Division of Developmental Medicine, University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK

Correspondence

W.S. Leslie
Human Nutrition
Division of Developmental Medicine
University of Glasgow
Glasgow Royal Infirmary
10 Alexandra Parade
Glasgow G31 2ER
UK
E-mail: w.s.leslie@clinmed.gla.ac.uk

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Abstract

Objective To determine the current practices in relation to weight management currently provided for overweight/obese patients attending different secondary care outpatient clinics. **Methods** Postal questionnaire sent to 100 consultant clinicians working in a range of specialist areas in three NHS Trust areas in Scotland, between January and March 2004. **Results** Overall response rate was 55%. Only 9% (five) of clinicians reported having a protocol in place for the management of patients who were overweight or obese. Lack of expertise and inaccessibility to expertise were cited frequently as reasons for having no protocol in place. Fifty-one per cent felt that weight management (including obesity treatment) should be undertaken by a specialist service either run by general practitioners (GPs), or by clinicians in a secondary care setting. Around a third of all those surveyed reported willingness to incorporate obesity management within their own routine specialty practice. **Conclusion** Clinicians acknowledged the adverse health effects of obesity within their specialist area, but felt unskilled and under-resourced to provide effective management. Effective prevention and management are required to challenge the obesity epidemic and will require the involvement of both primary and secondary care NHS settings. It is encouraging that a third of respondents felt prepared to incorporate obesity and weight management within their routine specialist practice.

Introduction

The estimated cost to the health service of obesity and related conditions, compared with people with ideal or normal weight, is immense (NAO 2001) and the development of strategies for the prevention and treatment of obesity and overweight is now a priority for health promotion and education (DoH 1992; WHO 1998). Given the large numbers of overweight and obese subjects (43% and 22% of the entire adult UK population) and its wide variety of clinical manifestations, it is recommended that

weight management should usually be undertaken in primary health care, community or commercial sectors (SIGN 1996). Attempts are being made to establish a structured approach to weight management in the primary care setting as a recent audit has shown that both the identification of obesity and overweight and its subsequent management are at present suboptimal (Counterweight Project Team 2004a).

In addition to being a major health problem in its own right, obesity contributes to a range of comorbid conditions, importantly including type 2 dia-

Table 1 Reasons for not having a formal weight/obesity management protocol

Reasons	n (%) [*]
Weight/obesity management not a priority for health care in general	5 (9.1)
Weight/obesity management not important to this specialist area	7 (12.7)
Expertise not available to treat weight/obesity management within this specialist area	21 (38.2)
Personnel skilled in weight management inaccessible	13 (23.6)
Weight/obesity management best undertaken by dedicated secondary care obesity specialist service	13 (23.6)
Weight/obesity management should be undertaken by a GP specialist service	15 (27.3)
Other	11 (20.0)

^{*}Column greater than 100% as more than one reason could be given per person.

- 'previous attempts at a weight management strategy in a general surgery context has often proved fruitless, we now just get on with it'; and
- 'waiting times to see dietitian, and I find that most patients attending dietitian are not motivated enough to lose weight'.

Recording of height and weight

Both height and weight were reported as being routinely recorded in outpatient clinics in just over half the responses (52%). Weight only was measured in a further 5% of cases. The outpatient clinics not measuring height and weight, and so unable to calculate body mass index, included: orthopaedics, general surgery, obstetrics/gynaecology, gastroenterology, respiratory medicine, general medicine, colorectal surgery, upper gastro intestinal (GI) surgery, cardiology and urology.

Action taken by the clinician if they considered a patient to be overweight/obese

Overall, if a patient was considered overweight or obese, referral to the hospital dietitian was the most frequently selected option (Table 2). This included the clinicians who reported having a protocol in place and also those who did not routinely measure patient's height and weight. Among those who selected this option, 25 indicated that this would be their only course of action, whilst 10 indicated that they may also refer a patient back to their GP for treatment. Very few clinicians said that they would take no action. Referral to a specialist obesity physician was not considered by any of the clinicians.

Table 2 Current management if patient considered overweight/obese

Management	n (%) [*]
Refer to hospital dietitian for your area	41 (74.5)
Refer to clinical nurse specialist	1 (1.8)
Refer to obesity specialist physician	0 (0.0)
Refer back to GP for management	15 (27.3)
Refer to commercial slimming organization	2 (3.6)
No action	3 (5.5)
Other referral	9 (16.4)

^{*}Column greater than 100% as more than one option could be chosen.

Almost all consultants (94.4%) agreed that overweight/obesity affected outcomes and treatment within their area of expertise. This included all those who said that weight/management was not a priority for health care in general and the majority who said it was not important to their specialist area (71.4%).

About one in five consultants responded that they were happy to prescribe anti-obesity drugs, however, 81.5% said they would not currently be comfortable prescribing them within their own specialist practice. A number of reasons were given for this, the most frequently cited being lack of experience in the use of these drugs. Other reasons for not using these drugs included:

- 'patients' need to consume less calories not take drugs at the NHS's expense';
- 'does not treat the cause of obesity which is a basic arithmetic problem – calories in more than calories out';
- 'no confidence in these methods, believe lifestyle modification is the cornerstone of management

and antiobesity drugs should be dealt with by a specialist’;

- ‘patients’ treated with drugs would need follow-up and I cannot follow-up patients for weight management purposes alone’; and
- ‘I do not have the time or inclination to manage obesity within my specialty’.

About twice as many clinicians chose Model B (identify and refer to a specialist obesity clinic) than Model A (identify, treat and manage overweight/obesity within each medical subspecialty) as the model for potential development (64% vs. 31%, $P < 0.0001$, χ^2 test). Two consultants wanted neither model the additional comment from one being ‘no evidence either would work – waste of money’. On the other hand the view of another consultant was that ‘either model would represent an improvement, however, what was the evidence for either, and perhaps A, or B should be a locally performed trial’.

Discussion

It is forecast that by the year 2010 one-third of adults will be clinically obese (Williams 1999) and the costs to health care services are expected to rise to an estimated £3.6 billion (NAO 2001). The contribution of overweight to type 2 diabetes and metabolic syndrome is such that weight gain is overtaking smoking as a cause of coronary heart disease and cancers (House of Commons Health Committee 2004). The development of strategies for the prevention and treatment of obesity is now a high priority. Primary care is usually identified as the most appropriate setting for weight management (SIGN 1996; Royal College of Physicians 2004) and there is little NHS activity related to the management of obesity outside general practice (NAO 2001). Previous research has shown that obesity is common in many different outpatient clinics (Cleator *et al.* 2002) and contributes to pathology and distress in many ways. The present study was limited both geographically and in terms of the survey numbers. However, the consensus amongst a wide range of hospital specialists suggests that the views reported may reflect those nationally.

The present survey showed clearly that most hospital specialists recognise that obesity is contributing

to their patients’ ill health, but suggested that they perceive little value in weight management. This is at odds with the literature and may reflect the unrealistic goals of obese patients to become thin. Five to 10 per cent weight loss brings multiple health benefits (Goldstein 1992) and is now an internationally accepted target for the short-term weight loss phase of weight management (SIGN 1996; NIH 1998; Royal College of Physicians 1998). Taking the example of type 2 diabetes alone, which now affects 5–10% of all 60 years olds (SEDH 2000) and as much as 20–30% of older Asian groups (McKeigue *et al.* 1988), 5–10% weight loss with diet and exercise will reduce new diabetes by 58% over 4 years (Tuomilehto *et al.* 2001; Diabetes Prevention Program Research Group 2002). The addition of orlistat – a non-absorbable anti-obesity agent – reduces new diabetes by a further 38% over 4 years (Torgerson *et al.* 2004). Modest weight loss also improves lung function, reduces the frequency of sleep apnoea, alleviates osteoarthritis and improves ovarian function (WHO 1998). There are strong arguments for urging clinicians to incorporate weight management within their specialty practices.

Clinicians who reported having a formal weight management protocol in place were in the minority. None forwarded a copy of the protocol suggesting that it may not in fact be documented or formalised. The usual course of action taken by these clinicians if a patient was considered overweight/obese was referral to the hospital dietitian.

Most clinicians felt they could not currently provide weight management within their areas of specialisation and just over a quarter indicated that they would refer patients back to their own GP for weight management. However, previous research has shown that GPs also feel that they do not have the expertise or resources to manage obesity/overweight (Hankey *et al.* 2004). Training is clearly an issue as clinicians feel they do not have the necessary skills to treat those who are overweight/obese and it is acknowledged that ‘little has been done to expand nutrition into the core training of all health professionals’ (Royal College of Physicians 2004, pp. 46–47).

Identifying those who are overweight/obese is a crucial step in its management, and secondary care clinics are considered a good opportunity to identify patients (Cleator *et al.* 2002). In the present study

almost half of clinicians reported that height and weight were not recorded routinely at their clinics. Therefore the opportunity to identify and manage those who are overweight/obese is, in many cases, lost. Lack of expertise and/or access to expertise was commonly cited as a reason for not having a protocol in place. This may discourage clinicians from taking time to identify overweight/obese patients if they feel that effective management is not accessible or available.

There are clearly different ways forward. Most clinicians favoured Model B (identify and refer to specialist obesity clinic) for potential development. However, a third of respondents felt that they could valuably tackle obesity within their specialist practice. A low-cost approach would be to build on this substantial minority. The comment of one clinician that evidence for the development of either model was lacking and research was needed is pertinent. As there is no established model of best practice in specialist secondary care of obesity in routine NHS services (as distinct from isolated academic units) the best plan is to establish programmes on the basis of best available evidence, but with a closed-loop audit to permit improvements to be incorporated. This needs to be established on the background of better incentives to enhance the first-line management of obesity in primary care, for example, Counterweight (Counterweight Project Team 2004b). A specialist obesity service is about to be piloted within the Greater Glasgow Health Board area and will provide much needed evidence for the development of effective obesity management strategies in routine clinical care.

Conclusion

Effective prevention and management are required to challenge the obesity epidemic. This will require the involvement of both primary and secondary care NHS settings. While acknowledging the adverse effects of obesity in clinical practice, many clinicians still regard this as an area for which they feel unskilled and are under-resourced. It is encouraging that, despite this, about one-third of all consultants felt prepared to incorporate obesity and weight management within their routine specialist practice.

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