

The impact of weight loss programmes on disordered eating

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Abstract

The prevalence of obesity is increasing globally. Significant weight loss is an effective strategy to manage the condition, as well as manage conditions associated with obesity, like type 2 diabetes (T2D). However, alongside the prevalence of obesity and T2D, the prevalence of eating disorders is equally increasing globally. Eating disorders can be devastating for people who experience them, and they often co-exist with overweight/obesity and T2D, therefore offering weight loss treatments to this population could be considered risky. In 2020, NHS England announced the roll-out of the NHS Path to Remission programme for people living with overweight/obesity and T2D, which offered total diet replacement (TDR) targeted at significant weight loss and diabetes remission. Concerns on the impact of the programme on disordered eating emerged.

The research in this thesis aimed to investigate the impact of weight loss programmes, including TDR, on disordered eating. I initially conducted a systematic review and meta-analysis to explore the impact of weight loss programmes, either alone or paired with psychological support intervention or pharmacotherapy on disordered eating scores, regardless of baseline disordered eating status. I found that weight loss programmes were associated with a consistent reduction in disordered eating in the end of the intervention and at a further follow-up. In sub-group analyses, disordered eating scores reduced more in people with an eating disorder at baseline compared with people without high scores, and there was no evidence the association depended upon intervention type. The review only identified two studies using more rigid interventions like low-energy diet replacement, where I hypothesised the risks would be greater. As a result, I designed and conducted a non-inferiority randomised controlled trial, investigating the impact of a TDR programme on disordered eating scores in people living with overweight/obesity, T2D and disordered eating at baseline. Disordered eating and its impairment reduced significantly in the intervention arm compared to the control group, and so did depressive symptoms and diabetes distress. No participant was judged to be at high suspicion for having developed a new eating disorder. I also analysed recordings of the dietetic sessions

qualitatively, to identify similarities and differences in experiences of people participating in a TDR programme according to their disordered eating score trajectories.

Participants with worsening disordered eating scores or of variable pattern of change throughout the trial reported eating usually in response to emotions and boredom, and experiencing significant hunger during the TDR phase, as well as a non-supporting environment. This often resulted in non-adherence and unsuccessful attempts to return to the programme. Participants who experienced stable or reducing disordered eating scores throughout the trial also experienced hunger but were often able to manage it and continue on the programme. Combining qualitative and quantitative data from this research, I concluded that weight loss programmes including TDR, are associated with reductions in disordered eating scores in the short term; longer term impact could be explored in future research.

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Finally, I attended an Oxford BRC-funded 3-day writing retreat to write part of Chapter 3 presented in this thesis.

The views expressed in this thesis are my own and not necessarily those of the NHS, Novo Nordisk UK Research Foundation, the University of Oxford or the Department of Health and Social Care.

Statement of contribution

I declare that this thesis is entirely my own work, completed under the supervision of Dr Paul Aveyard, Dr Dimitrios Koutoukidis, Professor Rebecca Park and Professor Susan Jebb, at the Nuffield Department of Primary Care Health Sciences, University of Oxford. I have led all projects presented in this thesis, including the design, conduct, and analysis of all studies, as well as the writing of Chapters and related journal manuscripts. I received feedback on all chapters presented in this work from my supervisors.

I, Dr Koutoukidis, Dr Paul Aveyard and Professor Rebecca Park contributed to the systematic review protocol presented in Chapter 2. Nia Roberts, the research librarian, helped me improve my search transcripts; I conducted the searches on my own, set up the project on Covidence and developed the data extraction sheet. Gina Wren and Dr Heather Tong acted as the second reviewer and assessed the risk of bias tool with me. Dr Koutoukidis assisted me in the analysis of the systematic review.

Myself, Dr Koutoukidis, Dr Paul Aveyard and Professor Rebecca Park contributed to the development of the trial protocol and the study materials presented in Chapter 3. Dr Koutoukidis has provided feedback on the intervention materials I developed described in the appendices. Erin Amor has contributed significant administrative support in distributing and overlooking the follow-up surveys of the study for the final year of my DPhil, as well as sending thank-you vouchers to participants. Dr Koutoukidis has assisted me in the analysis of the data, with input from Dr Aveyard.

All tables and figures contained within this thesis are of my own creation, unless stated and referenced otherwise. I hereby declare that no part of this thesis has been previously submitted for any other degree at this or any other University. Parts of this thesis have been previously published or submitted for publication as peer-reviewed journal articles.

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Abbreviations

AE	Adverse event
AI	Artificial Intelligence
ARIADNE	The impAct of low-eneRgy total dIet replAcement with behavioural support for remission of type 2 Diabetes oN disordEred eating
BED	Binge eating disorder
BES	Binge eating score
BMI	Body Mass Index
BMJ	British medical journal
BP	Blood pressure
BWL	Behavioural weight loss
CBT	Cognitive behavioural therapy
CIA	Clinical impairment assessment
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CUREC	Central University Research Ethics Committee
DiRECT	Diabetes Remission Clinical Trial
DMEC	Data monitoring and Ethics committee
DROPLET	Doctor Referral of Overweight People to Low Energy total diet replacement Treatment
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Eating disorder
EDE	Eating disorder examination
EDE-Q	Eating disorder examination questionnaire
EDNOS	Eating Disorder Not Otherwise Specified
eGFR	Estimated Glomerular Filtration Rate
GP	General practitioner
HbA_{1c}	Glycated haemoglobin
HCP	Healthcare professional
ICB	Integrated care board
ID	Identification
IBT	Intense behavioural therapy
IMD	Index of multiple deprivation
ITT	Intention to treat
Kg	Kilogram(s)
LCD	Low-calorie diet
NEWDawn	New remission care pathway: Diabetes Adaptive Weight management Network
NHS	National Health System
NICE	National Institute for Health and Care Excellence
PAID	Problem areas in diabetes
PHARMA	Pharmacological interventions
PHQ-9	Patient health questionnaire
PIS	Participant information sheet
PPI	Patient and Public Involvement
PSYCH	Psychological interventions

RCT	Randomised control trial
REC	Research ethics committee
SAEs	Serious adverse events
SCOFF	Sick, Control, One, Fat, Food
SD	Standard deviation
SE	Standard error
SMD	Standardised mean difference
T2D	Type 2 diabetes
TDR	Total diet replacement
UK	United Kingdom
USA	United States of America
VLCD	Very low-calorie diet
WS	Workstream

Chapter 1. Introduction

1.1 Pathophysiology and epidemiology of overweight/obesity

Overweight and obesity are defined as the excessive or abnormal accumulation of body fat that poses a risk to health[1]. A body mass index (BMI) over 25 categorises a person as overweight, and a BMI over 30 is used to determine obesity. The causes of obesity are complex; the Foresight report on "Tackling Obesities: Future Choices" identified 108 variables contributing to the development of the condition. These variables were grouped into seven themes: societal influences, food production, food consumption, biology, individual psychology, individual activity and activity environment[2]. The map depicting the interaction of these variables illustrates this complexity (Figure 1.1). Indeed, it is difficult to distinguish between nature and nurture, with estimates suggesting that around 70% of the variance in weight in adult life is due to genetics[3,4].

The prevalence of obesity in adults has doubled since 1990. It is estimated that 2.5 billion adults worldwide were living with overweight/obesity in 2022[5]. In England, around 15 million people live with obesity[6]. Obesity is associated with an increased risk of morbidity and mortality, predominantly due to cardiovascular disease and cancer[7,8]. Beyond the impact on individuals, obesity is estimated to cost wider society £27 billion annually. It also cost the NHS £6.1 billion in 2014/15, a figure projected to increase to almost £10 billion per year by 2050[9].

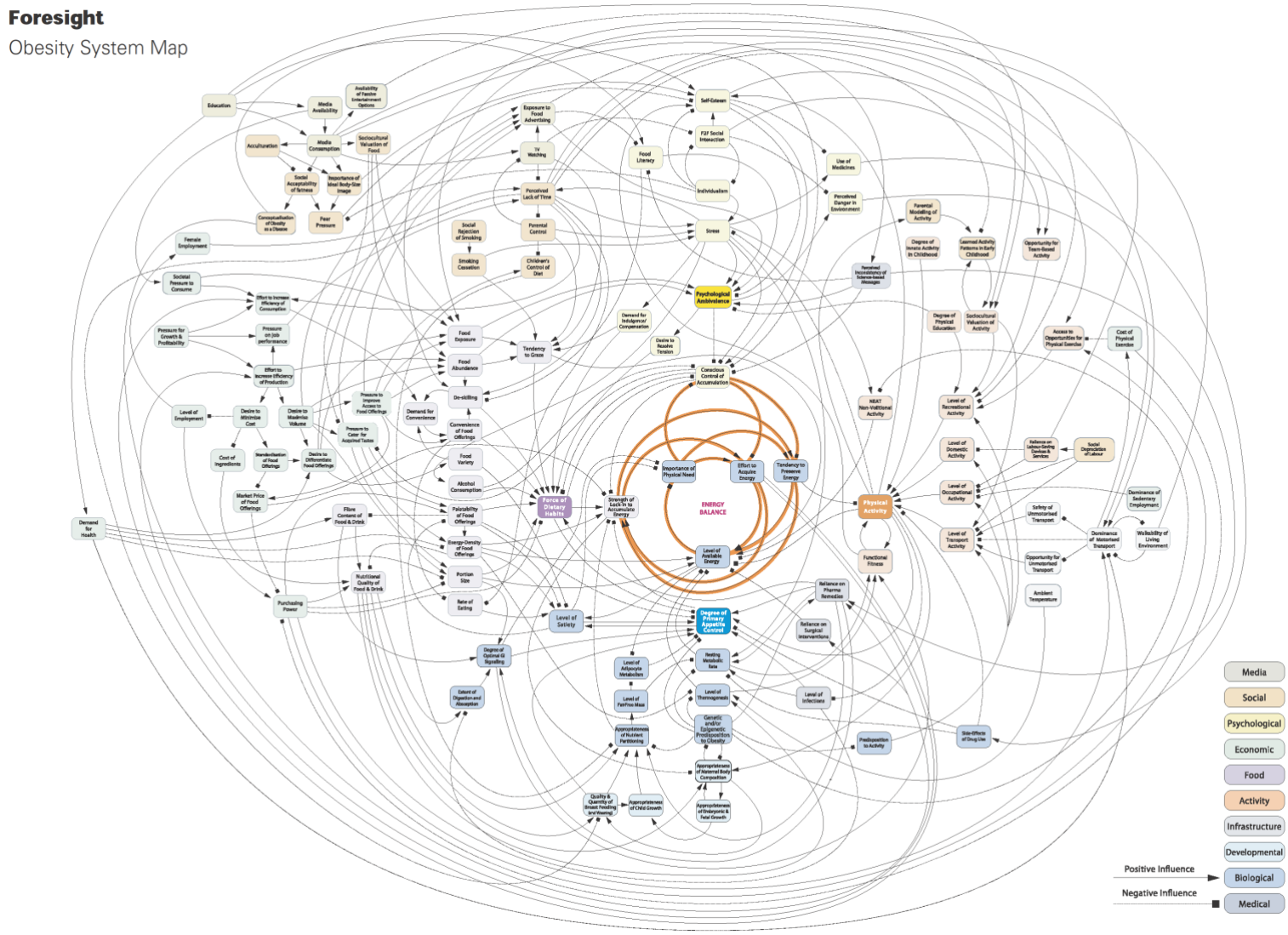
1.2 Pathophysiology and epidemiology of type 2 diabetes

Obesity is also the strongest risk factor for type 2 diabetes (T2D)[10,11]. T2D is one of the most common non-communicable diseases globally, with 437.9 million prevalent cases in 2019[12]; this number is projected to increase to 700 million by 2045[13]. More than 4 million people live with T2D in the UK alone[14]. T2D is a metabolic disorder caused by a combination of defective insulin secretion by pancreatic cells and insulin resistance, the inability of insulin-sensitive cells to respond to insulin[15]. While T2D has a strong genetic predisposition (family history, ethnicity), metabolic and environmental risk factors (such as obesity, sedentary lifestyle, and an unhealthy diet) also play a key role in its development and progression[16,17]. People of Asian, Chinese, Black African and Black Caribbean

heritage are 2 to 4 times more likely to have diabetes than people of White heritage[18]. Additionally, there is an inverse linear association between BMI and the age of T2D diagnosis[19].

In terms of diet, chronic consumption of a Western dietary pattern, characterised by foods high in energy, carbohydrates, and fat leads to elevated blood glucose levels and an increase in very-low-density lipoproteins, chylomicrons and their triglyceride-rich remnants. This results in low-grade inflammation due to an increase in reactive oxygen species. Chronic low-grade oxidative stress, which often co-exists with obesity significantly contributes to the pathogenesis of insulin resistance and T2D[20].

Figure 1.1. Full systems map, taken from Vandenbroeck IP, Goossens J, Clemens M. Foresight Tackling Obesities: Future Choices—Building the Obesity System Map. Government Office for Science, UK Government's Foresight Programme. 2018.



1.3 Management of obesity and type 2 diabetes

The National Institute for Health and Care Excellence (NICE) recommends a multicomponent approach to managing obesity, using behaviour change strategies to support weight loss. These interventions may include dietary modifications for energy restriction and physical activity, and in certain cases, pharmacotherapy[21]. Prevention of T2D can also be achieved through dietary modification, exercise, and weight loss, thereby treating excess weight first[22,23]. Individuals with obesity and comorbidities, such as T2D, who have previously made unsuccessful attempts to lose weight, may also be considered

for bariatric surgery under the same guidelines. In cases where excess body weight coexists with comorbidities like T2D, the BMI threshold for more intensive interventions may be lower.

T2D is routinely managed through dietary modifications and medication, which are typically offered in primary care as first-line treatments. Treatment protocols may vary based on geographic location and the time since diagnosis. According to NICE[24], patients with newly diagnosed T2D should be offered a structured education programme at diagnosis, with annual reinforcement and reviews. For people living with overweight/obesity and T2D, recommendations emphasise lifestyle changes, including diet and exercise, with or without medication. The first-line medication is usually metformin, and depending on how well blood glucose is controlled, medication might need to be up-titrated, either in terms of dose and/or by adding additional agents.

The cost of care for diabetes is at least 3.2 times higher compared to the average per capita healthcare expenditure, whereas it can rise up to 9.4 times more if there are complications[25]. With the increasing prevalence of T2D and disease progression in already diagnosed patients, the cost of treatment continues to rise. In England alone, the prescription of diabetes medication has increased from £420 million in 2015/16 to £880 million in 2022/23, an increase of 107%[26].

1.4 Type 2 Diabetes - Remission via treating overweight/obesity

Living and managing diabetes, along with its physical and mental health consequences, through medication is one option for patients. However, it is no longer the only option. In recent years, remission has become a feasible alternative, following the DiRECT study[27], which demonstrated that remission can be achieved through significant weight loss interventions delivered in primary care. Given that 90% of people live with overweight/obesity at the point of diagnosis[28], substantial weight loss can be an effective management tool for most individuals living with T2D.

According to Diabetes UK, T2D remission is defined as HbA1c < 48 mmol/mol (6.5%) for at least three months, without the need for diabetes medication[29]. This definition may vary slightly across different organisations and studies. Achieving disease remission is the top priority for patients, clinicians, and

policymakers,[30] as it improves quality of life, reduces morbidity[31] and lowers healthcare costs[32]. In the past, remission was primarily possible for patients undergoing bariatric surgery. Factors that predict remission after surgery include younger age, good glycaemic control at baseline, taking a small number of diabetes medication, absence of insulin treatment, and greater weight loss[33,34]. However, only a small percentage of patients qualify for surgery, and among those who do, just 0.002% undergo the procedure[35].

Total diet replacement (TDR) programmes with behavioural support, where people consume around 800-900 kcal/day in specially formulated food products, can induce remission of recently diagnosed T2D in almost half of the patients and be delivered cost-effectively in routine care[31]. The DiRECT study also demonstrated physiological changes as a result of significant weight loss; participants in the intervention arm achieving remission experienced some recovery of pancreatic volume and morphology[36]. The more significant the weight loss, the greater the likelihood of remission within the first year[37]. However, the long-term impact of short-term weight loss is still unclear, especially due to gradual weight regain, which may require the reintroduction of medication to manage T2D [38].

A pilot offering TDR with behavioural support in primary care to 10,000 people with T2D across England started in September 2020[39,40]. As of April 2024, these programmes are available throughout the country and are on track to become part of standard care for the treatment of T2D in the NHS. An evaluation of the programme is also underway, examining various aspects of its delivery and efficiency[41].

1.5 Mental health in overweight/obesity and type 2 diabetes

In addition to the physical health burden, obesity is also associated with a significant psychological burden. Living with excess weight has been associated with a 55% greater risk of developing depression[42], a 25% greater risk of developing mood and anxiety disorders[43], and lower quality of life[44]. A diagnosis of T2D can also have major implications for mental health[45]. Depression is more prevalent

in people living with T2D compared to those without (18% versus 10%)[46], and even minor psychological problems can negatively affect treatment adherence[47,48].

One of the primary contributors to poor mental health in individuals with obesity is the stigma they face[49]. A systematic review[50] found strong evidence that employees with obesity perceive disparities in employment and wages related to their weight, as well as weight bias in evaluations and hiring decisions. In addition, people with overweight/obesity reported stigmatisation in movies and television. The review also found moderate evidence of weight bias regarding healthcare treatment offered to people living with obesity, as well as bias from family members, friends and the media.

The stigma associated with living with T2D is also a major contributor to poor mental health, potentially due to the close relationship with excess weight, but also due to the common belief that the main factor in managing the condition is predominantly lifestyle modification. People living with T2D often report feelings of embarrassment at social events when offered unhealthy options that they feel compelled to refuse[51]. In one study, 84% of participants reported they believed their T2D to be stigmatising[52]. They associated negative stereotypes with their diagnosis, using terms like *"fat", "obese", "overweight", "lazy", "slothful", "couch potato", "over-eater", "glutton"*. Participants also reported missed opportunities in life, such as friendships that lapsed when friends were unsupportive, or missed work opportunities. Stigma is also perceived to be present among healthcare professionals[52]. Essentially, T2D and obesity seem to share many of the same stigma principles[50,53,54].

Beyond stigma, a longitudinal study found that people with T2D experienced a fivefold increase in reports of poorer quality of life and higher odds of psychological distress following diagnosis[55]. Diabetes UK recommends that all patients living with diabetes have access to psychological support to reduce diabetes-related distress and improve self-management of the condition[56].

1.6 Eating disorders, disordered eating, T2D, and obesity

Eating disorders are psychiatric conditions that affect one's relationship with eating and body image. These disorders are diagnosed using the *Diagnostic and Statistical Mental Disorders* (DSM, 5th edition)

criteria[57]. Eating disorders have amongst the highest morbidity and mortality of any psychiatric condition[58], imposing significant costs on both individuals and healthcare systems. The global prevalence of eating disorders has doubled since the early 2000s[59], with lifetime prevalence of around 8% in women and 2% in men. This increase has coincided with the rise in obesity prevalence and both bulimia nervosa and binge eating disorder (BED) are often comorbid with obesity and/ or contribute to it[60,61]. Eating disorders, particularly BED and night eating syndrome, are more prevalent in people with obesity than people with a healthy weight[62]. In Australia, for example, the prevalence of obesity with comorbid binge eating has increased sevenfold in the past 20 years[63].

BED was first described under the umbrella of eating disorders otherwise described (EDNOS) in the DSM criteria published in 1994[64], but became a separate eating disorder in the 2013 DSM-V criteria[57]. To receive a BED diagnosis, a person must experience episodes of binge eating with loss of control, occurring recurrently and causing distress, in the absence of compensatory behaviours. BED is the most common eating disorder[60], and its diagnosis is associated with high rates of psychiatric and physical comorbidities[65]. BED is also independently associated with a higher risk of physical health comorbidities like chronic pain, chronic headaches, hypertension[60]. It's not just diagnosed BED though; eating disorders have been previously described as a continuum[66,67].

It is important to distinguish between eating disorders and disordered eating. While eating disorders meet the strict diagnostic criteria of the DSM, disordered eating refers to a suboptimal relationship with body image and eating that does not meet these criteria. However, experiencing disordered eating increases the risk of experiencing an eating disorder later on[68,69]. Disordered eating is often marked by behaviours stemming from specific psychopathology, leading to psychosocial impairment[57], such as avoiding social events that revolve around eating (e.g. a friend's birthday dinner, a work lunch), or experiencing emotions like shame, guilt, and anxiety related to food.

Many individuals with disordered eating or concerns about body image may not meet the criteria for an eating disorder but may still engage in restrictive practices to control their weight, which can cause significant distress. It's also crucial to distinguish between binge eating (which is a behaviour

experienced in various eating disorders and is a symptom of disordered eating) and BED, a diagnosable eating disorder, which doesn't share the same psychopathology as other EDs do[70]. This psychopathology is characterised by overvaluation of control in eating, weight and shape, and is common to both bulimia and anorexia nervosa.

T2D alone is associated with an increased risk for BED and depression[71,72]. BED is the most frequently diagnosed ED in people with T2D[71]. This association is not surprising, as disordered eating is prevalent in people living with obesity/overweight, and given that T2D is also prevalent in the same population, T2D and disordered eating often co-exist. In addition, management of T2D includes a large focus on changing dietary habits, sometimes drastically, meaning good management (or lack of it) is strongly associated with controlling one's diet. Understandably, this focus can lead to "perfectionist" attitudes towards eating; this is the case at least in type 1 diabetes[73]. Often, people with T2D express feeling deprived and often exercise rigid control of their diet as the sole way of losing weight and managing their condition[74]. As a result, according to various studies[75-78], 2.5% to 40% of people living with T2D experience some form of disordered eating, with 1 in 5 women with T2D reporting binges, compulsive overeating or excessive food intake[75].

1.7 Weight loss and disordered eating

Weight loss therapies are integral in the management of overweight/obesity and T2D. However, this population is at high risk of poor mental health and disordered eating. Therefore, what is the association between weight loss and disordered eating?

The first historical concern that energy restriction (or in other words dieting) can lead to negative psychological consequences, including disordered eating and depressive symptomatology was documented in the infamous Minnesota Starvation Experiment[79]. Apart from experiencing extreme negative emotions like depression, irritability and anger, some participants in this study also developed binge eating that in some cases persisted when access to food was restored. Conclusions from this study in people within the normal BMI range cannot entirely be extrapolated to people living

with overweight and obesity, as their energy stores are different and their start-up point for weight loss is higher. In addition, energy restriction advocated during behavioural weight loss (BWL) is considerably milder.

One of the components of concern in weight loss programmes is the notion of restraining one's eating. Dietary restraint[80] refers to the cognitive effort to eat less than someone would like to[81]. It is different to dieting, which is the behavioural outcome of dietary restraint, although the terms are sometimes used interchangeably in research. Dieting, as measured by dietary restraint scales has been deemed integral in the development of eating pathology in various aetiological models of eating disorders[70,82]. However, when coupled with successful weight management strategies, engaging in moderate levels of dietary restraint resulted in a decrease in obesity and eating disorder risk[83,84].

More recent theories on the development of eating disorders have identified a correlation between dietary restraint and overeating, often alongside body dissatisfaction[85,86]. It may also be that there are other factors, such as genetics, that predispose an individual to eating disorders and the practice of dietary restraint is the trigger, regardless of the amount of that individual's self-regulation[87]. Indeed, restraint in isolation, without other aspects of eating disorder psychopathology is rather limiting in determining one's risk, as restraint alone increases in individuals with overweight/obesity as they lose weight successfully[88,89].

Another component of concern in weight loss programmes is the emphasis on body weight. A theoretical model investigating the development of EDs combining three different theories (sociocultural[90], dietary[91] and affect regulation[92]), posits that pressure to be thin and internalisation of thinness contributes to body dissatisfaction, as an impossible ideal to obtain. This then fosters dieting and negative affect, with bingeing/eating providing comfort from negative emotions, which subsequently increases the risk of EDs[82]. Body dissatisfaction has been associated with efforts of controlling eating behaviours and its subsequent connection to eating disorder psychopathology[93,94].

Combining the factors of dietary restraint and body dissatisfaction, the spiral model[95] theorised that people with body dissatisfaction (not necessarily overweight/obesity) often take up dieting. The failure to achieve the results they anticipate can lead to low self-esteem, which can then trap them in a vicious circle of dieting and restriction. Other sociocultural models suggest that thinness is glorified in Western societies, leading to internalisation and body dissatisfaction in susceptible people. Failure to achieve the said thin body through dieting is perceived as a personal failure, ignoring the fact that these standards are nearly impossible to meet[96]. Therefore, the cycle of restraint and bingeing is sustained, in addition to building up in the psychopathology.

According to the cognitive behavioural theory[70], eating disorders or disordered eating results from overvaluation of the control of eating, weight and or shape , which can lead to body dissatisfaction and prompts an individual to impose rigid rules to achieve a certain weight or shape. Efforts to adhere to extreme and highly specific rules can break down, for example at times of negative emotion, and temporary abandonment of the rules, which then leads to overeating and low self-esteem and even more rigid rule formation.

Based on the theories mentioned above, a theoretical basis exists for how weight loss programmes could trigger disordered eating. In addition, there have also been observations that dieting precedes the development of disordered eating symptoms[91,97]. However, what actually happens when disordered eating psychopathology is directly measured during participation in a weight loss programme? A 2020 systematic review and meta-analysis of weight loss programmes versus no intervention showed that behavioural weight management programmes reduced symptoms of depression and increased mental health-related quality of life at both intervention end and at one year from baseline[98]. However, evidence on disordered eating was sparse, with one study showing no evidence of an effect on binge eating, emotional eating (four studies), and body image dissatisfaction (two studies). Data were too imprecise to be sure that no effect was present. A more recent systematic review found that despite weight regain after BWL, there was no evidence of mental health harm and some evidence of improved mental health at and after the programme end[99]. The latter found no clear

evidence of a between-group difference at any time point on measures of body image and eating disorders but included only seven studies.

A 2014 systematic review on the effect of severe energy restriction using total and partial meal replacement programmes on binge eating found 10 eligible trials (5 with pre-post designs)[100]. The limited evidence did not allow for a meta-analysis. For people without binge eating at baseline, scores overall appeared to increase. On the other end of the spectrum, among people with clinically diagnosed binge eating disorder at baseline, reductions in average binge eating scores were observed after the dietary intervention. In mixed samples (both people with and without binge eating behaviours at baseline), disordered eating seemed to reduce. However, in studies with people with subclinical disordered eating, the direction of the effect was less clear. A recent systematic review and meta-analysis, excluding interventions using pharmacotherapy and weight loss programmes delivered to treat eating disorders like binge eating (therefore excluding some people with a diagnosis of binge eating at baseline), showed that there was an overall reduction in disordered eating at the end of the intervention, in pre-post analysis[101].

Nevertheless, weight is often perceived as a sensitive topic, and raising the subject of weight loss is avoided by doctors due to its perceived negative consequences[102]. The DiRECT[27] and the DROPLET[103] studies and then the rollout of TDR in the NHS brought the potential negative psychological impact of weight loss on disordered eating back into the spotlight. Despite their promising pathophysiological benefits, TDRs are anecdotally considered even more rigid than traditional weight loss programmes. This could be due to their restrictive nature of replacing all food with formula products for a significant amount of time, and/or their history. Low and very low-calorie diets (LCDs and VLCDs respectively) started being used in the 1970s, and peaked during the 1980s when their use subsequently reduced, mainly due to their formulations leading to medical complications[104]. Indeed, healthcare professionals are still hesitant to offer them to patients, partly to avoid negative psychological impact[105], and anecdotally, due to fears that these regimes could trigger eating disorders. This is in line with more

and more discussions in the public sphere around "diet culture" and the impact of weight loss on the risk of developing disordered eating in recent years[106].

1.8 Summary of research gaps

Obesity and T2D prevalence are increasing globally. Significant weight loss is an effective strategy to avoid the detrimental effects of obesity, and also achieve diabetes remission in people with T2D and overweight/obesity. TDR with behavioural support can be pursued effectively in primary care.

However, along with the prevalence of obesity and T2D, the prevalence of eating disorders is equally increasing globally. Eating disorders can be devastating for people who experience them, and they often co-exist with overweight/obesity and T2D. As a result, there are a lot of concerns that a programme like the NHS Path to Remission being offered to many patients in primary care might cause a significant proportion of people to worsen their existing disordered eating or develop an eating disorder, especially given that people with T2D are particularly at risk.

1.9 Aims and objectives of this thesis

This work attempts to understand the impact of weight loss on disordered eating, using T2D and a TDR weight loss programme similar to the NHS Path to Remission as the vehicle. More specifically, I will attempt to:

- Investigate the impact of weight loss interventions on disordered eating in a systematic review and meta-analysis
- Assess if TDR offered with behavioural support can increase the risk of being diagnosed with an eating disorder in susceptible people living with T2D and overweight/obesity, at the end of the intervention
- Investigate how disordered eating scores evolve throughout the intervention and why

Table 1.1. Research questions and study design

Work Stream	**Research questions**	**Design**
WS1	What is the effect of behavioural weight management programmes on disordered eating?	Systematic review, meta-analysis
WS2	Is TDR non-inferior to standard care for scores of disordered eating in people with T2D scoring high for eating disorder psychopathology?	Non-inferiority randomised controlled trial
WS3	How do TDRs affect behaviours related to disordered eating?	Qualitative analysis of recorded intervention sessions with participants using content analysis

Chapter 2. The impact of weight loss interventions on disordered eating: a systematic review & meta-analysis

This chapter has been submitted as a manuscript to eClinicalMedicine journal and is currently under review.

2.1 Summary

It is unclear whether weight loss interventions worsen disordered eating. I aimed to systematically evaluate the association between weight loss interventions and disordered eating.

Six databases were searched from inception until May 2022. Trials of weight-loss interventions in people with overweight/obesity were included if they reported a validated score for disordered eating: the Eating Disorder Examination Interview (EDE) or the Eating Disorder Examination Questionnaire (EDE-Q). Interventions included BWL programmes and pharmacotherapy licenced for weight loss, with or without concurrent psychological support. Pooled standardised mean differences in scores of disordered eating were calculated using random effects meta-analyses. Risk of bias was assessed using the Cochrane risk of bias (RoB 2) tool and the Newcastle-Ottawa scale for randomised and single-arm trials, respectively.

Thirty-one studies with 53 eligible arms (26 BWL, 8 BWL + pharmacotherapy, 18 BWL + psychological intervention, 1 pharmacotherapy + psychological intervention) and 2,730 participants were included. The mean weight change was -4.8kg (95%CI: -5.9, -3.7). Compared with baseline, disordered eating scores changed by -1.49 standardised mean difference (SMD) units (95%CI: -1.71, -1.27, $p<0.001$, $I^2=94\%$) at intervention completion (median of 6 months). Four randomised trials that directly compared a weight loss intervention to no/minimal intervention reported an improvement of -0.56 SMD units (95%CI, -0.99, -0.13, $p<0.01$, $I^2=48\%$) that was not maintained at further follow-up. In sub-group analyses (a) disordered eating scores reduced more in people with an eating disorder at baseline compared with people without high scores, (b) there was no evidence the association depended upon intervention type, and (c) disordered eating scores reduced more in trials appraised as at low risk of bias.

Despite heterogeneity in effect size, weight loss interventions were consistently associated with a reduction in disordered eating scores. These findings provide reassurance that weight loss interventions do not worsen disordered eating, at least in the short term, and may even improve it.

2.2 Introduction

Several systematic reviews, mentioned in Chapter 1, have provided imprecise evidence suggesting a potential benefit of participating in BWL programmes on eating disorder symptoms. However, these reviews excluded studies with interventions targeting eating disorders alongside weight loss or using weight loss pharmacotherapy or were not able to conduct meta-analyses[100,101].

Accordingly, I undertook a systematic review to assess the impact of weight loss interventions with or without pharmacotherapy and/or psychological support, on the risk of developing an eating disorder, regardless of baseline disordered eating status or type of weight loss intervention.

2.3 Methods

The review protocol was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42023404792)[107]. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysed (PRISMA) reporting guidelines[108].

2.3.1 Study selection- Eligibility criteria

Randomised controlled (RCT), randomised comparative, and single-arm trials of weight loss interventions were included if they recruited adults (≥18 years) with overweight/obesity (as defined in the original publications), with or without disordered eating or eating disorders at baseline. Studies that included participants with both healthy and excess weight were included only if they reported results in the subgroup of those with overweight/obesity at baseline. BWL programmes had to prescribe energy restriction with an explicit weight loss goal[109]. Psychological interventions had to include widely used psychological treatments aimed at weight loss and lasting at least 4 weeks, like cognitive behavioural therapy (CBT), or interventions developed and/or delivered by psychologists/therapists/mental health professionals (or relevant students). Pharmacotherapy

interventions were those licensed for obesity treatment (or those that share a class effect) in the UK. Behavioural weight loss programmes could be combined with pharmacotherapy and/or psychological support to manage disordered eating and thereby reduce weight.

Interventions focusing solely on exercise/physical activity without energy restriction were excluded, as it was outside the scope of this review.

Equally, studies on weight loss with bariatric surgery were excluded. A systematic review showed that even though disordered eating behaviours often subside post-surgery, for a subgroup they persist or even develop ab initio [110]. Given the lack of a randomised control group in bariatric studies, it is unclear whether the development of such behaviours is the effect of surgery or would have occurred regardless of surgery. In addition, measuring disordered eating post-bariatric surgery is particularly complex, and the same tools used in the general population are not always reliable, as they are no longer fit for purpose[110,111]. The physiological changes patients undergo change eating patterns and make typical consumption difficult or impossible. Therefore, pooling results from bariatric and non-bariatric populations in a single review was deemed to not be appropriate as the populations are likely to be too dissimilar to allow for meaningful comparisons.

There was no restriction on the length of follow-up of participants. Studies were required to report disordered eating in either a global score and/or sub-scale scores using the Eating Disorder Examination (EDE) Interview or the Eating Disorder Examination Questionnaire (EDE-Q), and I extracted all available scores.

For comparative trials, the comparators could be usual care, minimal-intensity interventions for weight loss, or waiting list control. Usual care was determined in the context of what is usually offered in routine care by non-specialist staff (e.g. publicly available resources on diet and weight loss). If studies had arms described as “usual care” but offered specialist advice and/or referral to structured programmes, these were included as active interventions. Studies in animals, children and/or adolescents, on people with obesity due to genetic conditions (e.g. Prader-Willi syndrome), or after

bariatric surgery, or pharmacotherapy used off-label for weight loss (e.g. antidepressants) were excluded.

2.3.2 Data sources and searches

MEDLINE, Embase, PsycINFO, CINAHL, Cochrane Central Register of Controlled Trials and Web of Science were searched from inception until 16/05/2022, using relevant terminologies to capture: "weight loss/weight management", "obesity/overweight", "disordered eating/eating disorders". An indicative search strategy for the database of Embase can be found in Appendix 2.2. Searches were not restricted by country or language. References of systematic reviews identified through searches and of the included studies were screened.

2.3.3 Data extraction

The Covidence software was used for abstract and full-text screening[112]. Extraction was performed into a pilot-tested and bespoke extraction sheet in Microsoft Excel. Along with two colleagues (GW/HT), we screened titles and abstracts, and full texts for inclusion. I performed the data extraction with HT independently and another independent reviewer (GW) checked 50% of the extractions for accuracy. Any conflicts in screening or extraction were resolved by discussion, or by referral to a third reviewer. Study authors were contacted for further data and/or clarifications if needed.

The outcomes at the end of the intervention and post-intervention follow-up were extracted where the latter took place at least six weeks after the end of intervention. Body weight was also collected.

2.3.4 Quality assessment

Risk of bias for randomised clinical trials was assessed by myself and a colleague (GW), using the Cochrane risk of bias tool[113] and the Newcastle Ottawa scale for observational studies[114]. Risk of bias was assessed based on randomisation sequence generation, allocation concealment, blinding of outcome assessment, and attrition bias. It is not possible to blind participants or study personnel in behavioural intervention trials, therefore this domain was not assessed. Studies were judged at high risk of attrition if less than 75% of participants were followed up at the end of the intervention. Blinding of outcome assessment was judged as high risk if EDE interviews were done by study

members who were aware of the participants' allocation. Outcomes captured through self-reported EDE-Q were deemed low risk. I assessed publication bias with funnel plots.

2.3.5 Data synthesis

Given eligible studies included both EDE-Q and EDE scores, I calculated the standardised mean difference by dividing the difference in the mean disordered eating score pre- and post-intervention by the standard deviation of the change[115]. When estimating the SD of change, I assumed the baseline and follow-up values were correlated based on published data[116]. I repeated this process for the EDE-Q/EDE subscales. In some studies, only mean subscale scores were reported, without the mean global score; I therefore calculated the mean global score by dividing the sum of the mean subscale scores by the number of subscales. I conducted a post-hoc sensitivity analysis excluding these studies. I included analyses that imputed missing data where available. To reduce bias in summary estimates, I included studies regardless of whether the outcome showed significant change at follow-up.

Where studies only reported BMI, I calculated weight using mean height by sex for the specific country[117].

The pooled estimates were based on outcomes of similar endpoints and the pooled estimates are presented as mean differences with a 95% confidence interval (CI) for continuous variables. The minimum number of studies for quantitative synthesis in a meta-analysis was set at three. Statistical heterogeneity was assessed using the I^2 statistic tool[118], with 0-24% indicating no heterogeneity, 25-49% low, 50-74% moderate and 75-100% high heterogeneity.

2.3.6 Statistical analysis

I used random-effects models because of the expected heterogeneity in the interventions and study populations. Meta-analysis was conducted for single-arm trials pre and post-intervention, and separately for meta-analysis of randomised control trials comparing weight loss interventions with no active treatment separately, using the Hartung–Knapp–Sidik–Jonkman approach applied to the DerSimonian–Laird simple method of moments estimator to obtain less biased estimated effects and 95% CIs[119]. For 3-arm RCTs, participants in each of the 2 interventions were compared against half of

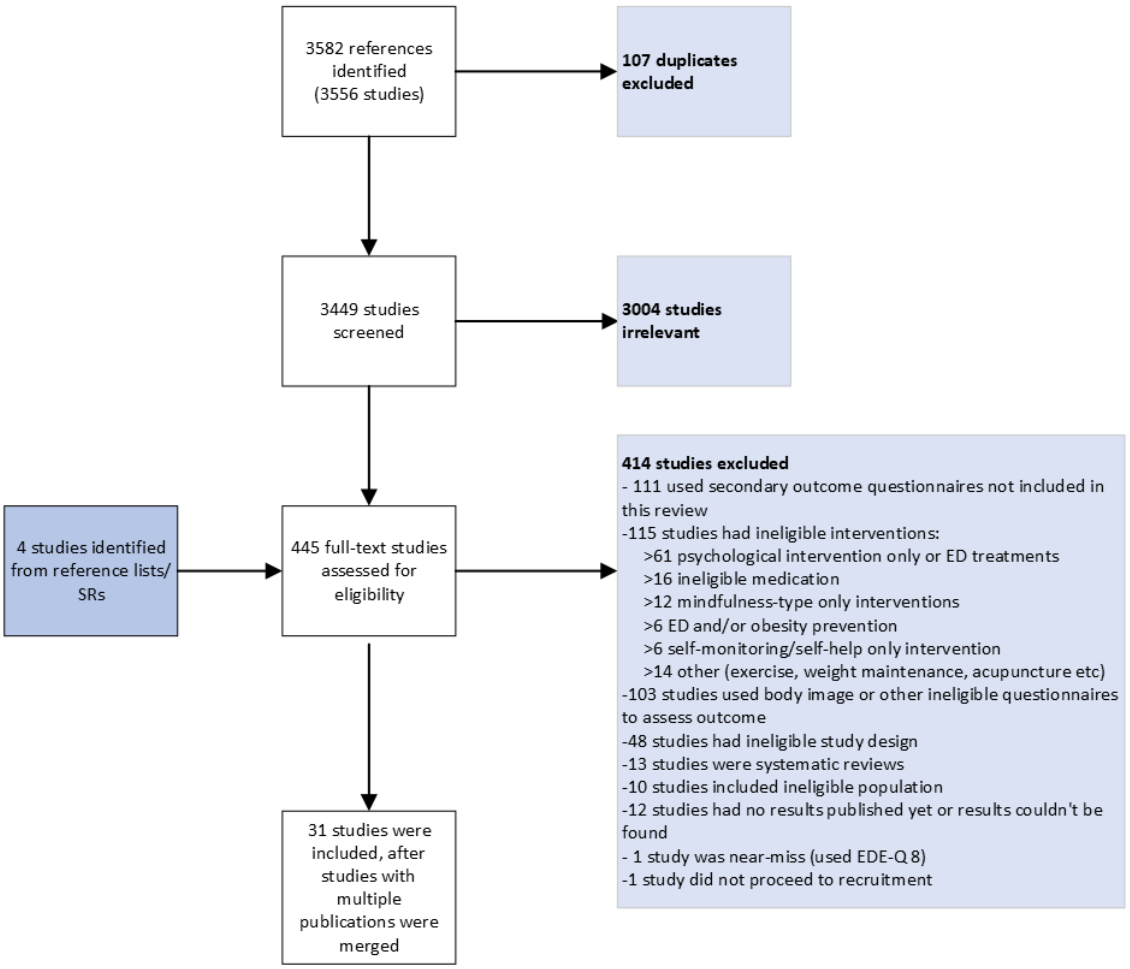
the participants in the control group. Outcomes are summarised as difference in means with 95% CIs, both for SMD in disordered eating scores as well as weight in kg.

I ran 2 pre-specified sub-group analyses: (1) a sub-group analysis based on the type of intervention (BWL versus BWL+ pharmacotherapy versus BWL+ psychological support) and (2) a subgroup analysis based on the baseline status of disordered eating. For the latter, I classed baseline disordered eating based on reported eligibility criteria as people with or without eating disorders. If not specified, I classified the population as not having an eating disorder, if the mean EDE/EDE-Q score reported at baseline was <2.67, or as unselected for eating disorders, if it was at least 2.67[120]. I undertook a post-hoc subgroup analysis based on the overall risk of bias score. I conducted a meta-regression of the association between weight change and change in disordered eating scores. All analyses were conducted in R Studio, version 4.3.2.[121]

2.4 Results

The literature search identified 3,556 records and 446 references were full-text screened, with 31 studies included (Figure 2.1). Twelve studies were ongoing and/or had not published results prior to December 2022.

Figure 2.1. PRISMA flow diagram



2.4.1 Study and participant characteristics

The 31 trials included 2,730 participants and reported on 53 eligible arms, including 4 randomised controlled trial arms, plus their 4 respective control groups. The number of participants per intervention arm ranged from 12 to 167, with a mean of 45 per arm. Twelve studies were conducted in Europe and the UK, 18 in North America and one in South America (Table 2.1).

Table 2.1. Characteristics of the included studies

Study & country	**Total, No (at baseline)**	**Arms**	**Presence of disordered eating at baseline**	**Outcome assessment tool**	**Duration, mo**	**Next follow-up post-intervention completion**
Berk et al., 2018 [122] The Netherlands	83	Very low-calorie diet (VLCD)+ cognitive behavioural therapy (CBT)	No	EDE-Q	18m (higher intensity up till ~6 months)	24 months
	75	VLCD				
Grilo et al., 2005 [123] USA	25	Orlistat + CBT *(ED treatment)*	Yes	EDE, subscales	3 months	6 months
	25	CBT + moderate weight loss diet *(ED treatment))*			3 months	
Wilfley et al., 2002 [124] USA	81	CBT and mild weight loss therapy *(ED treatment)*	Yes	EDE (manually converted by sub-scales), subscales	6 months	10 months
Calugi et al., 2016 [125] Italy	54	Residential weight loss therapy + CBT	No	EDE, subscales	~ 1 month intensive and then as an outpatient (in total 6 months)	N/A
	54 (BED)		Yes			
Carbone et al., 2021 [126] Italy	23 (BED)	Naltrexone-Bupropion + mild weight loss diet *(treatment for altered eating*	Yes	EDE-Q, subscales	4 months	N/A
	20		No			

		behaviour + weight loss)				
Carels et al., 2021 [127] USA	26	Behavioural weight loss + self-compassion skills training	No	EDE –Q (manually converted by sub-scales), subscales	3 months	N/A
	28	Behavioural weight loss	No			
Chao et al., 2019 [128] USA	50	Behavioural weight loss therapy	Population unselected by ED	EDE-Q, subscales	6 months	12 months
	50	Intensive Behavioural weight loss therapy + liraglutide				
	50	Intensive Behavioural weight loss therapy with 12-week low calorie diet + liraglutide				
daLuz et al., 2017 [129] Brazil	50	Mild weight loss + enhanced CBT *(ED treatment))*	Yes	EDE-Q	6 months	12 months
*DalleGrave et al., 2020 [130] Italy	67	Weight loss + group CBT	No	EDE-Q	18 months	N/A
Mensinger et al., 2016 [131] USA	40	Weight loss programme	No	EDE-Q, subscales	6 months	24 months
Di Marco et al., 2009 [132] USA	20	Standard guided self-help weight loss + motivational interviewing	No	EDE-Q subscales, EDE-Q (manually converted by sub-scales)	3 months	N/A
	19	Standard guided self-help weight loss				
Grilo et al., 2021	12	Naltrexone and	Yes	EDE-Q	3 months	6 months

[133] USA		buproprion +lifestyle modification				
	10	control (placebo)				
Grilo et al., 2005 [134] USA	38	Behavioural weight loss + guided self-help *(ED treatment)*	Yes	EDE-Q subscales, EDE-Q (manually converted by sub-scales)	3 months	N/A
	15	control (minimal intervention)				
Dassen et al., 2018 [135] the Netherlands	51	Weight loss + cognitive training	No	EDE-Q	~ 1 month	7 months
	40	Mild weight loss				
Grilo et al., 2013 [136] USA	20 (BED)	Orlistat + behavioural weight loss	Yes	EDE, subscales	4 months	6 months
	20 (BED)	Behavioural weight loss +placebo				
	20	Orlistat + behavioural weight loss	No			
	19	Behavioural weight loss +placebo				
Abiles et al., 2013 [137] Spain	49 (BED)	Mild weight loss+ CBT	Yes	EDE-Q subscales, EDE-Q (manually converted by sub-scales)	3 + 12 months	N/A
	61 (non-BED)		No			
Grilo et al., 2020 [138] USA	47	Moderate weight loss therapy + orlistat	Yes	EDE	6 months	N/A
	46	Moderate weight loss therapy + placebo				
	39	Moderate weight loss therapy				

Loader et al., 2013 [139] UK	18	Behavioural weight loss + guided bibliotherapy self -help	Population unselected by ED	EDE-Q subscales, EDE-Q (manually converted by sub-scales)	6 months	N/A
	18	Behavioural weight loss				
Nauta et al., 2000 [140] the Netherlands	21	Behavioural weight loss	No	EDE-Q subscales, EDE-Q (manually converted by sub-scales)	~4 months	10 months
	16 (BED)		Yes			
Grilo et al., 2011 [141] USA	45	Behavioural weight loss	Yes	EDE, EDE subscales	6 months	12 months
	35	Sequential CBT + behavioural weight loss *(ED treatment)*			10 months	
Masheb et al., 2011 [142] USA	25	Low-energy density diet *+ CBT (ED treatment)*	Yes	EDE, EDE subscales	6 months	N/A
	25	Nutrition counselling + CBT *(ED treatment)*			6 months	
Munsch et al., 2007 [143] Switzerland	36	Behavioural Weight loss therapy	Yes	EDE subscales, EDE (manually converted by sub-scales)	4 months	N/A
Pataky et al., 2018 [144] Switzerland	35	Multidisciplinary weight loss programme + CBT/coaching	Population unselected by ED	EDE-Q, subscales	12 months	N/A
	39					
	13					
Preuss et al., 2017 [145] Germany	28	Weight loss therapy with impulse control	Population unselected by ED	EDE-Q	~ 3 months	6 months

*Ramirez et al., 2001 [146] USA	40	Weight loss programme	No	EDE-Q Restraint and Eating Concern only	4 months	N/A
	48	Weight loss and body image therapy				
Rock et al., 2010 [147] USA	167	Weight loss programme (telephone)	No	EDE	6 months more intensive phase, 2 years in total	12 months
	164	Weight loss programme (face-to-face)				
	111	Control (usual care)			6 months	
Barnes et al., 2017 [148] USA	30	Weight loss with motivational interviewing (online)	No	EDE-Q	3 months	6 months
	29	Nutritional psychoeducation				
	30	Control (usual care)				
Barnes et al., 2018 [149] USA	31	Motivational Interviewing and Nutrition Psychoeducation	No	EDE-Q	3 months	6 months
Moss et al., 2017 [116] Canada	69	Behavioural weight-loss programme + motivational interviewing	No	EDE-Q, subscales	3 months	9 months
	66	Behavioural weight-loss programme				
Werrij et al., 2009 [150] the Netherlands	96	Cognitive dietetic group treatment	No	EDE-Q, subscales	2.5 months	12 months
	104	Exercise and dietetic treatment				
Wilson et al., 2010 [151] USA	64	Behavioural weight loss	Yes	EDE	6 months	12 months
Dallegrave et al.[130] and Ramirez et al.[146] were not included in the meta-analysis.						

Twenty-one arms from 15 studies included participants with a diagnosis of an eating disorder, 27 arms from 17 studies excluded people with eating disorders, 9 arms from 4 studies were unselective. When paired with weight loss interventions, psychological interventions either targeted the treatment of disordered eating[123,124,126,129,134,141,142], or aimed to enhance weight loss through body image therapy[122,146] and self-compassion[139], for example. One study used CBT to help participants maintain weight loss[122].

Overall, 90% of participants were female, the mean age ranged from 38 to 55 years, and the mean BMI ranged from 30.5 to 46.1 (reported in 21 studies). Attrition ranged from 5% to 50% at the end of the intervention. The median duration of intervention was 6 months (range: 1-18 months) and for the further follow-up, the median duration was 9.5 months from baseline (6-24 months).

2.4.2 Single-arm trial analysis

In the pre-post design, 51 eligible interventions (arms) from 31 studies were included in the analysis of global EDE-Q/EDE scores. Two studies were not included because Ramirez et al.[146] only reported two of the four subscale scores and no global scores, whereas DalleGrave et al.[130] did not report SD of the mean global scores. In the pre-post meta-analysis, there was clear and consistent evidence of a reduction in EDE-Q (-1.49 SMD; 95% CI, -1.71 to -1.27; I^2=94%, n=52) (Figure 2.2) at the end of the intervention compared with baseline. This reduction was sustained at further follow-up (-1.54 SMD; 95% CI, -1.79 to -1.30; I^2=93%, n=33) (Figure 2.3).

Figure 2.2. Association between weight loss interventions and disordered eating at the end of the intervention, pre-post analysis of single arms

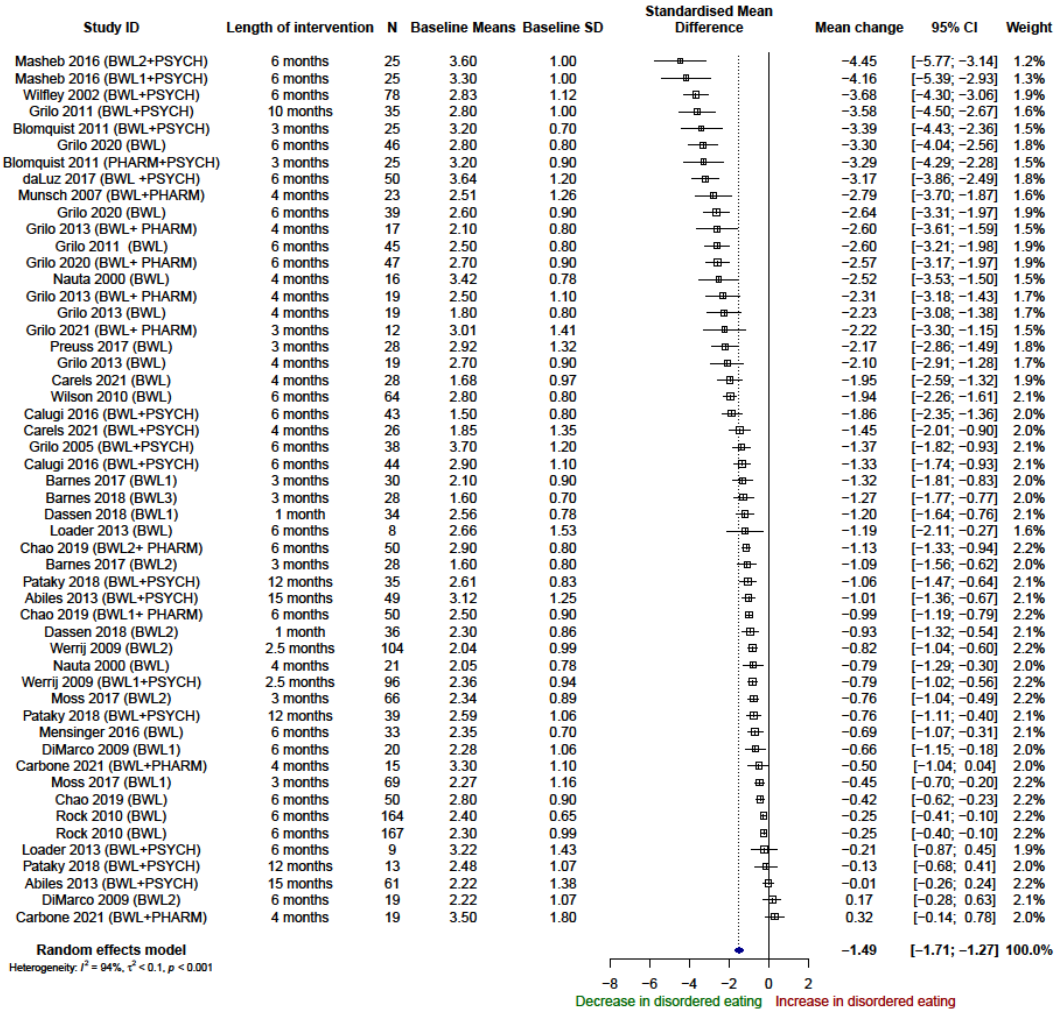
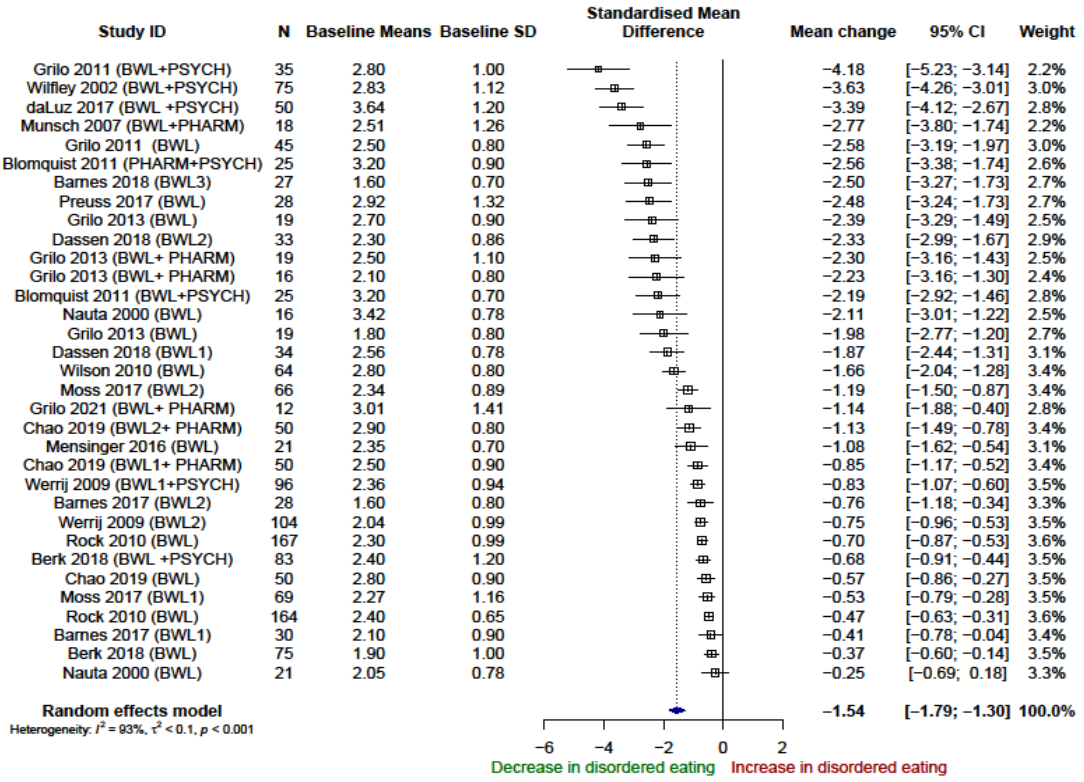


Figure 2.3. Association between weight loss interventions and disordered eating in the further follow-up, pre-post analysis of single arms



This was in the context of a mean weight change of -4.8kg (95% CI, -5.91 to -3.67; I^2= 98%, n=49) at the end of the intervention (Figure 2.4). Thereafter, there was mild weight regain with the mean weight change from baseline until further follow-up at -3.4kg (95% CI, -4.91 to -1.85; I^2= 96%, n=31) (Figure 2.5).

Figure 2.4. Weight loss at the end of the intervention, pre-post analysis of single arms

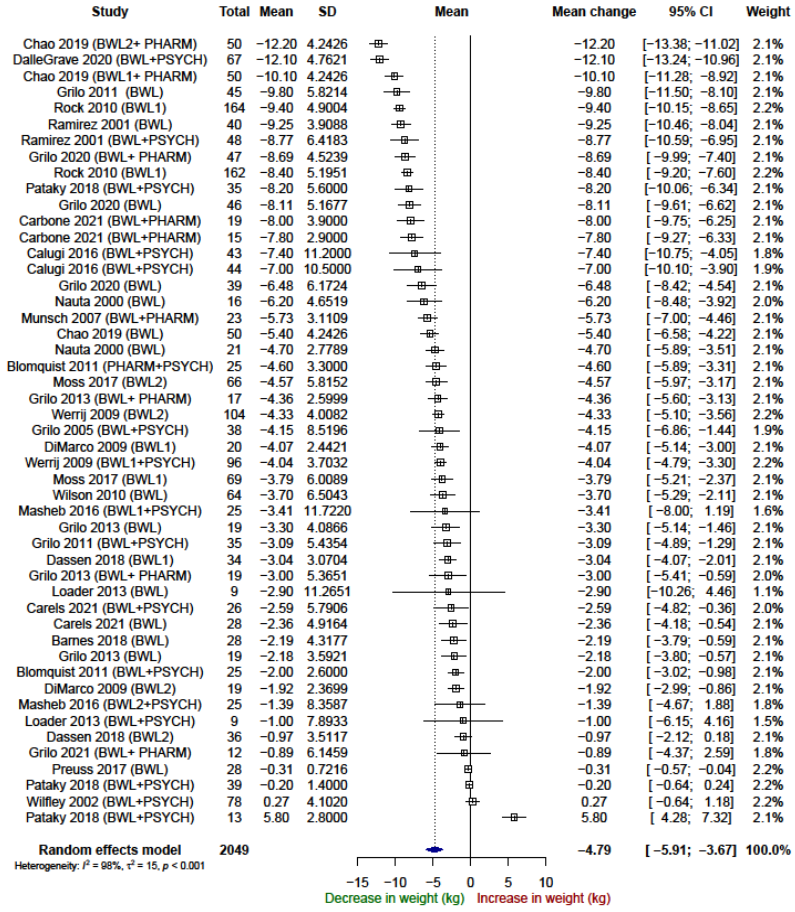
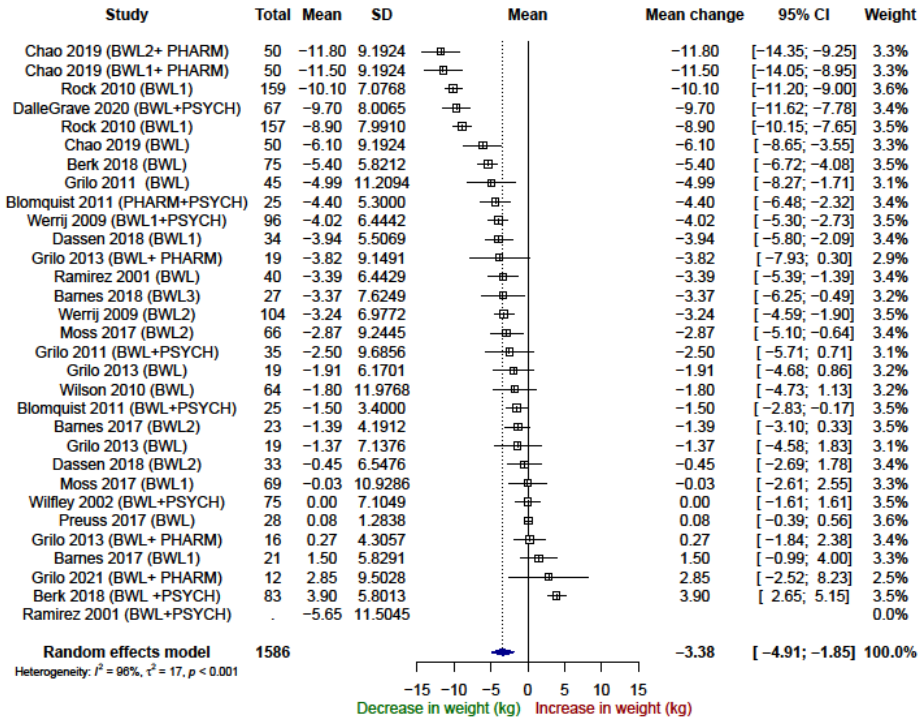


Figure 2.5. Weight loss in the further follow-up, pre-post analysis of single arms



Across the EDE-Q/EDE sub-scales, there was some evidence of a significant increase in dietary restraint (Figure 2.6), whereas there was clear and consistent evidence of a significant reduction in all other subscales (weight concern, shape concern, eating concern) at the end of the intervention (Figures 2.7, 2.8, 2.9). At further follow-up, there was no evidence that restraint differed from baseline (Figure 2.10), whereas there were still clear and consistent reductions in the other subscales (Figures 2.11, 2.12, 2.13).

Figure 2.1. Meta-analysis of restraint sub-scale at the end of the intervention, pre-post analysis of single arms

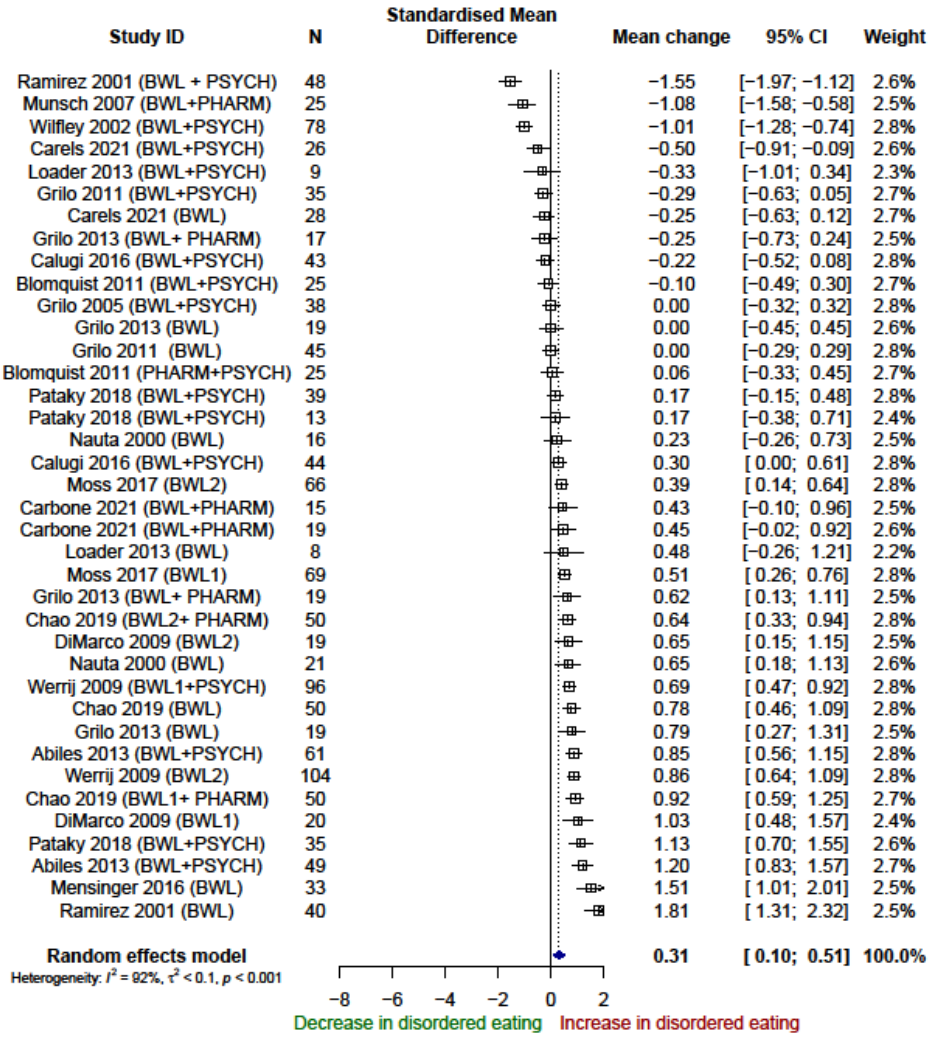


Figure 2.2. Meta-analysis of eating concern sub-scale at the end of the intervention, pre-post analysis of single arms

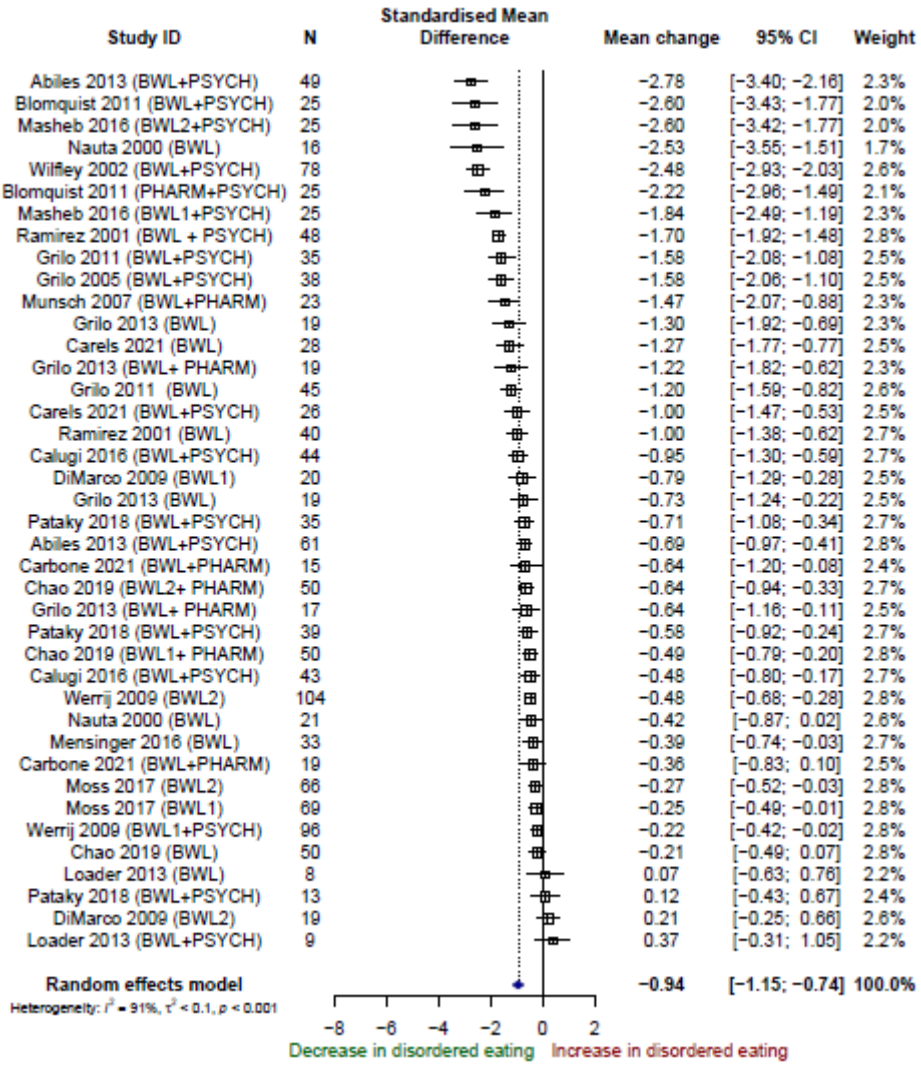


Figure 2.3. Meta-analysis of weight concern sub-scale at the end of the intervention, pre-post analysis of single arms

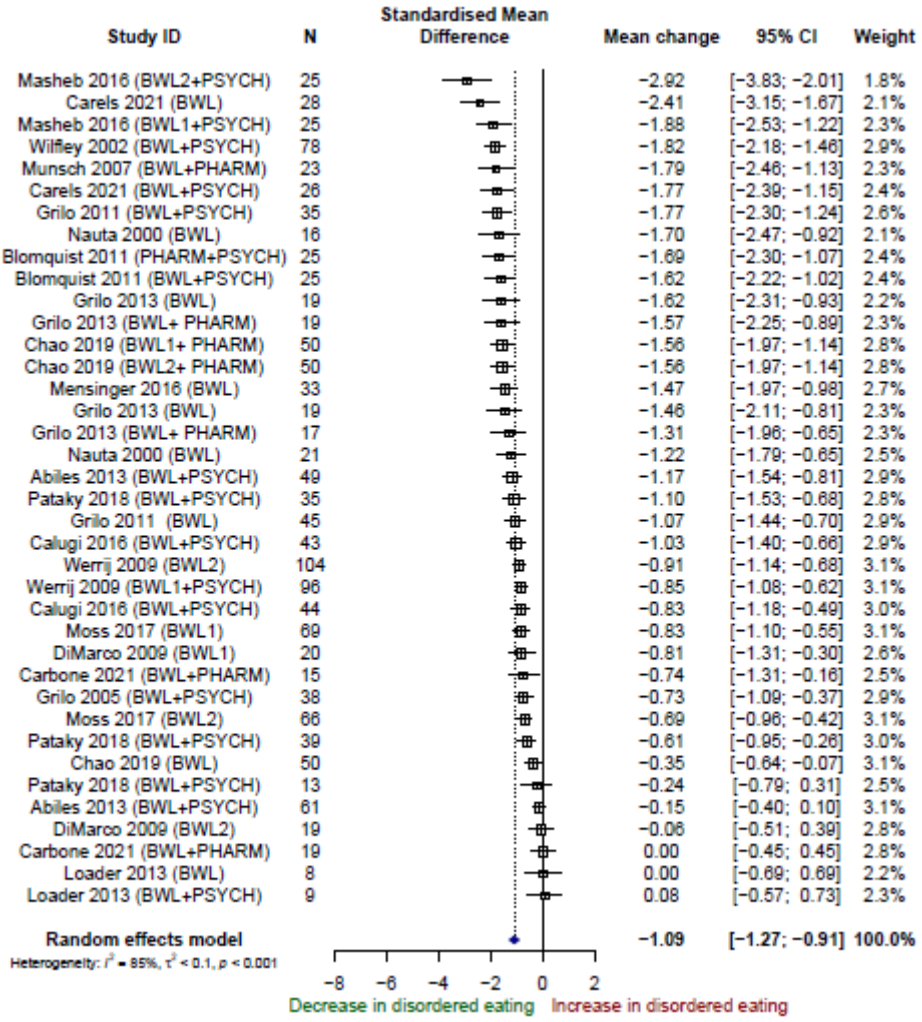


Figure 2.4. Meta-analysis of shape concern sub-scale at the end of the intervention, pre-post analysis of single arms

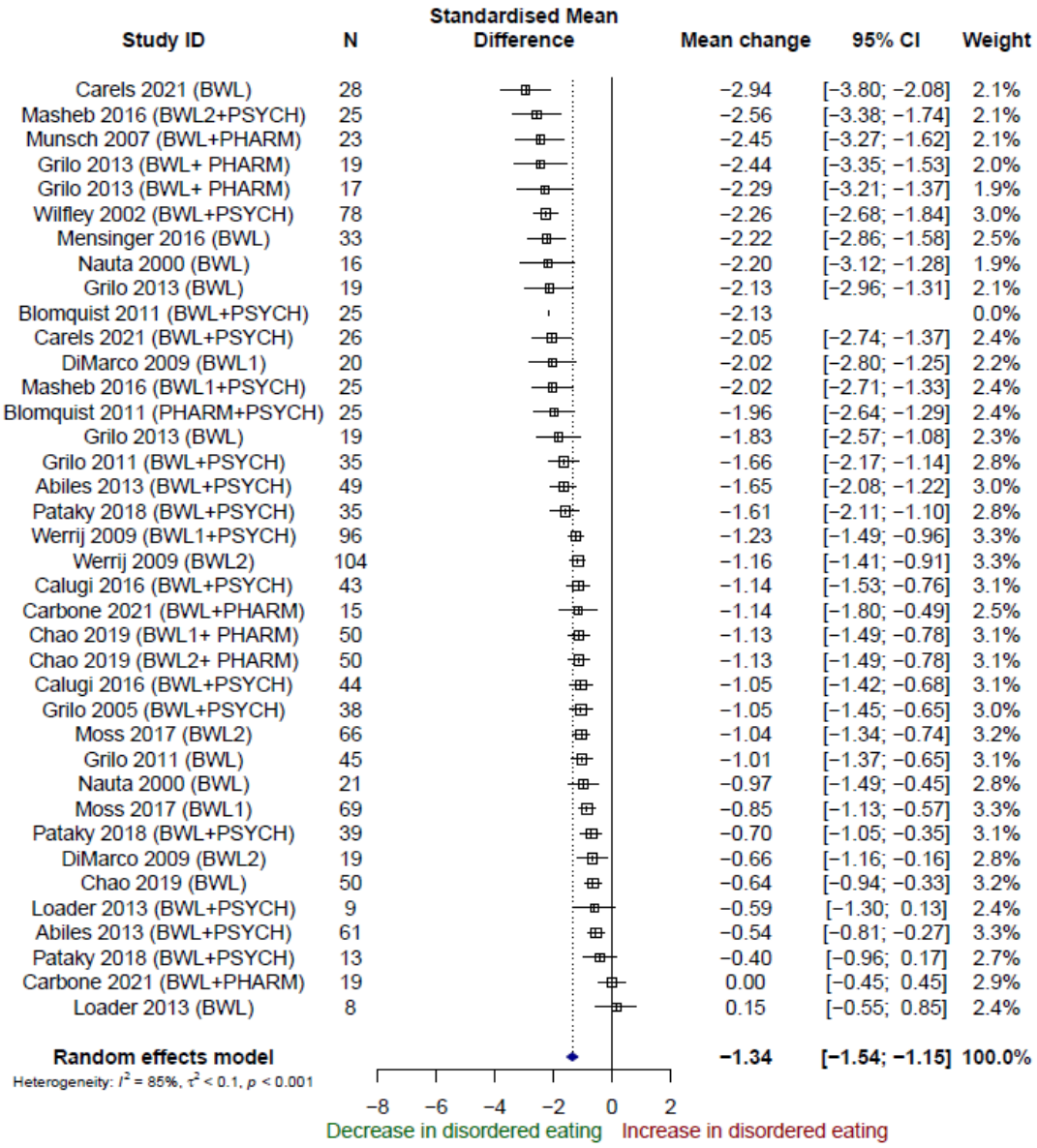


Figure 2.5. Meta-analysis of restraint sub-scale in further follow-up, pre-post analysis of single arms

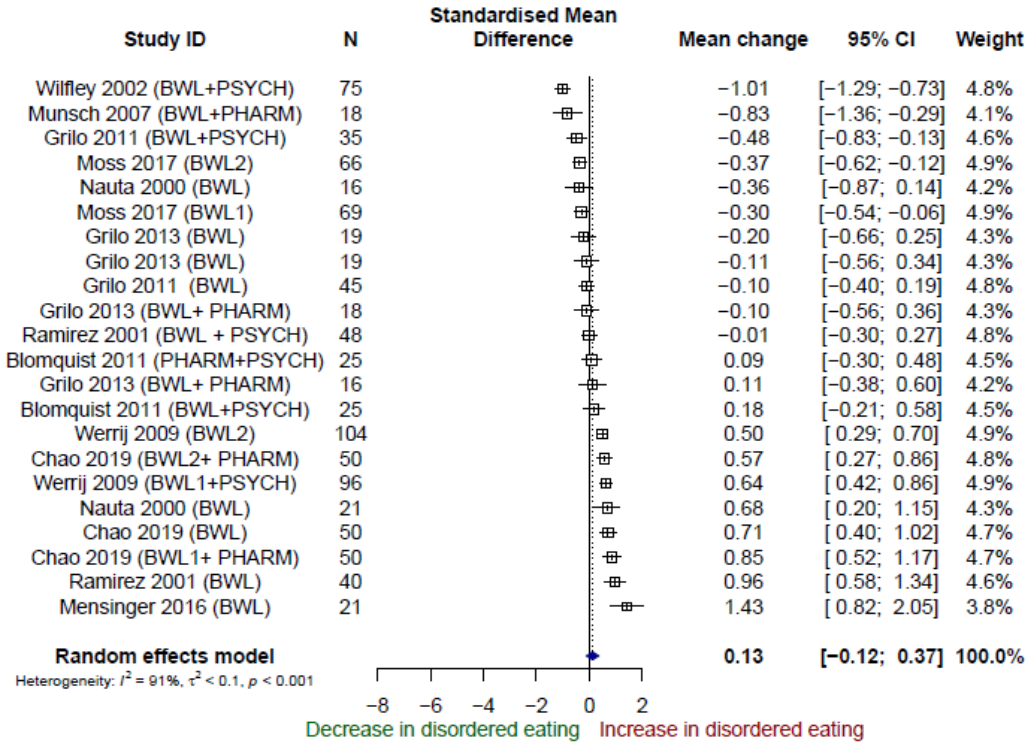


Figure 2.6. Meta-analysis of eating concern sub-scale in further follow-up, pre-post analysis of single arms

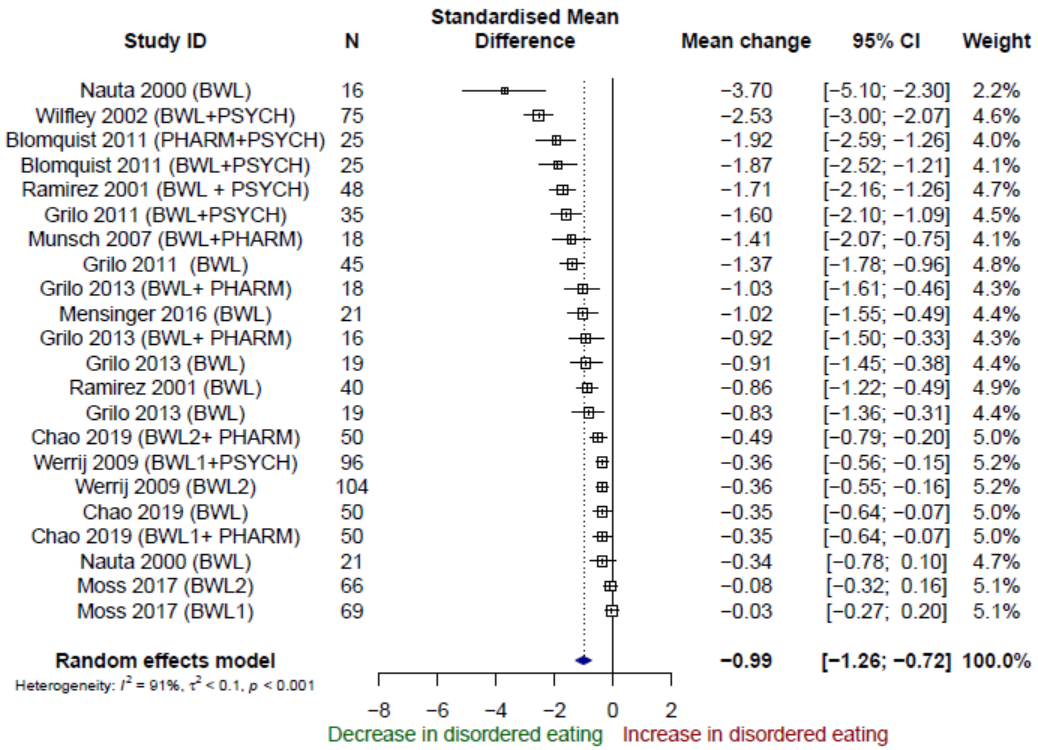


Figure 2.7. Meta-analysis of weight concern sub-scale in further follow-up, pre-post analysis of single arms

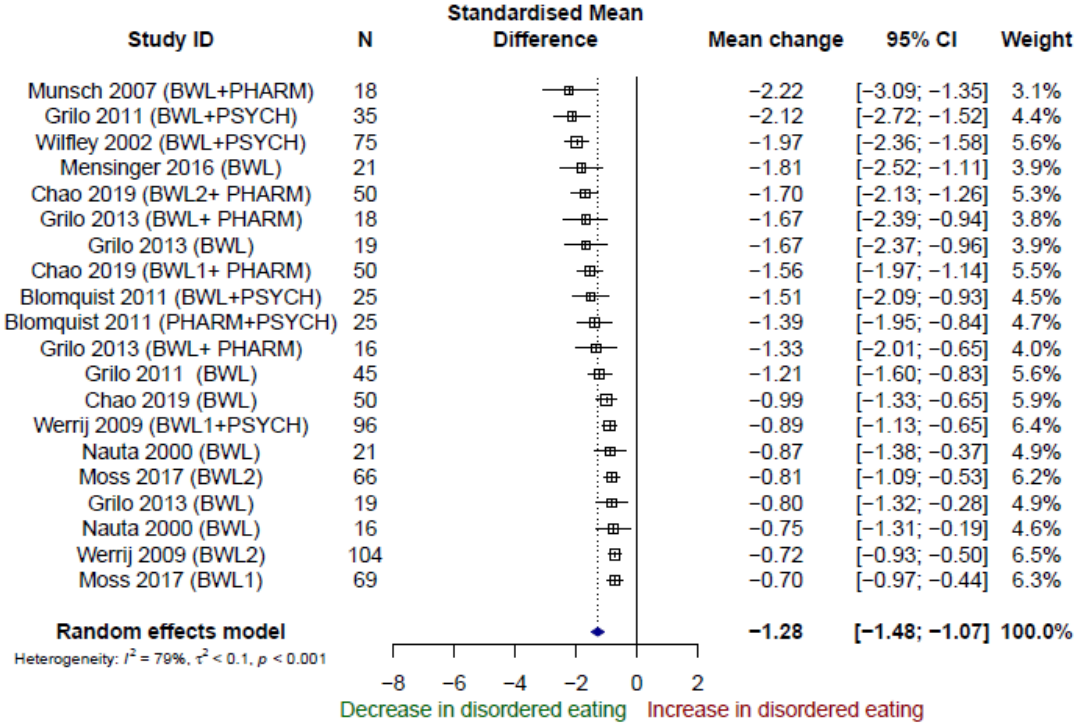
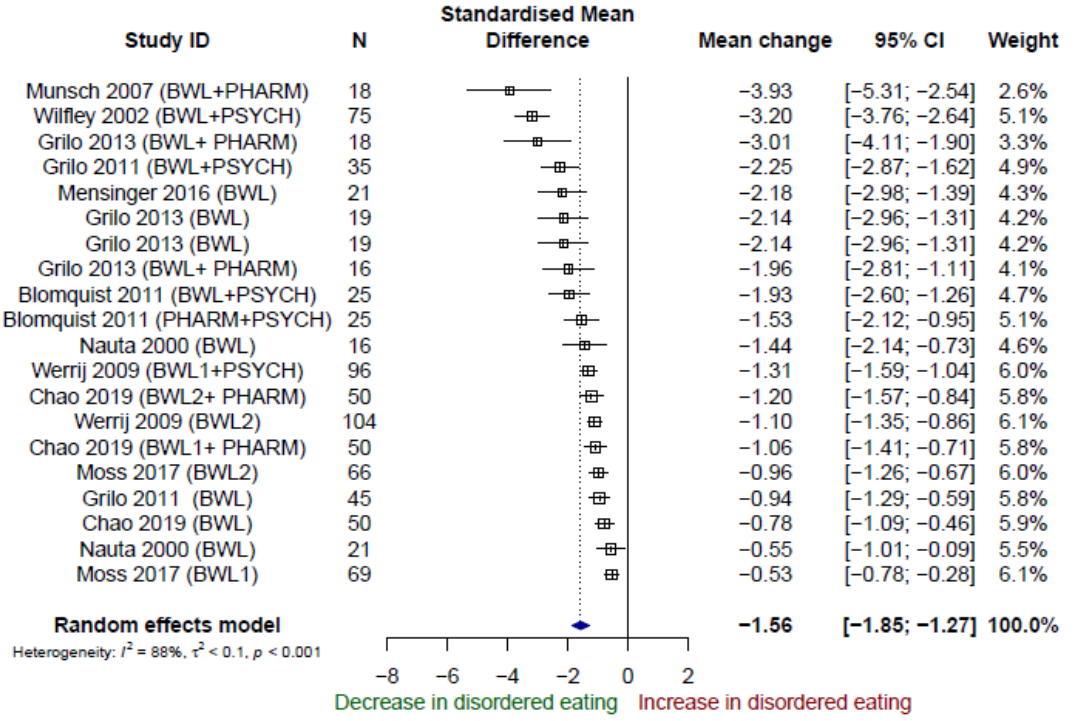


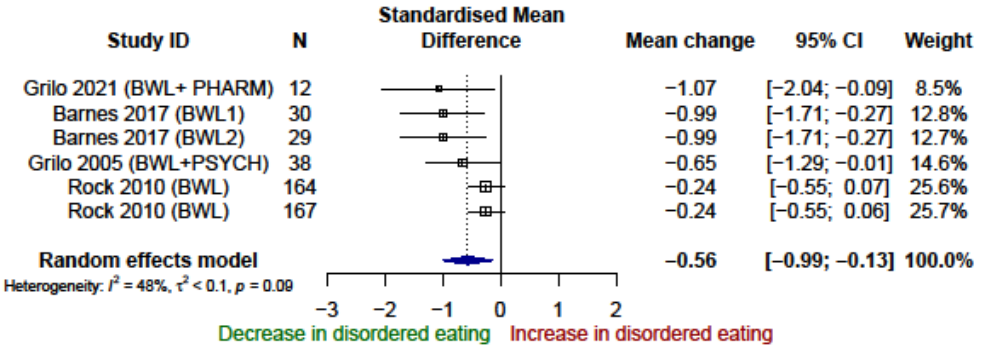
Figure 2.8. Meta-analysis of shape concern sub-scale in further follow-up, pre-post analysis of single arms



2.4.3 Randomised controlled trial analysis

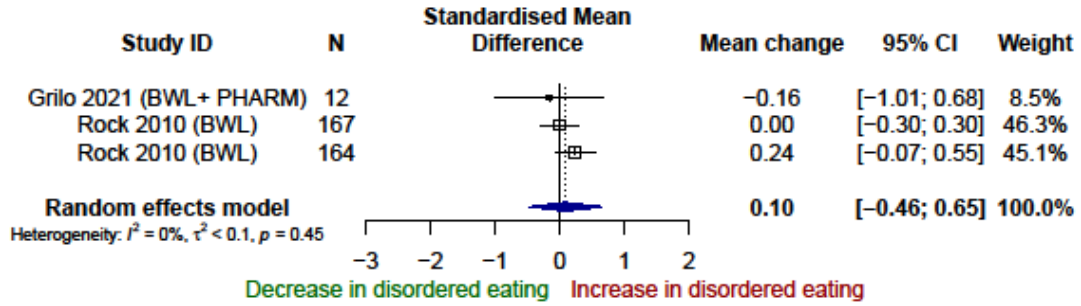
Four studies were included in the intervention versus control meta-analysis [133,134,147,148]. Control groups involved placebo without dietary intervention[133], self-monitoring diary of behaviours without intervention[134], offering publicly available printed resources on diet and exercise[147], and discouragement from starting a weight loss programme[148]. The end-of-treatment effect of weight loss programmes versus usual care/minimal intervention was -0.56 SMD; 95% CI, -0.99 to -0.13; I^2=48%, n=4) based on clear and consistent evidence (Figure 2.14).

Figure 2.14. Association between weight loss interventions and disordered eating at the end of the intervention, analysis of randomised control trials



Two studies followed up participants beyond the intervention end, and there was no evidence of an effect on disordered eating compared with control (0.10 SMD; 95% CI, -0.46 to 0.65; I^2=0%, n=3) (Figure 2.15).

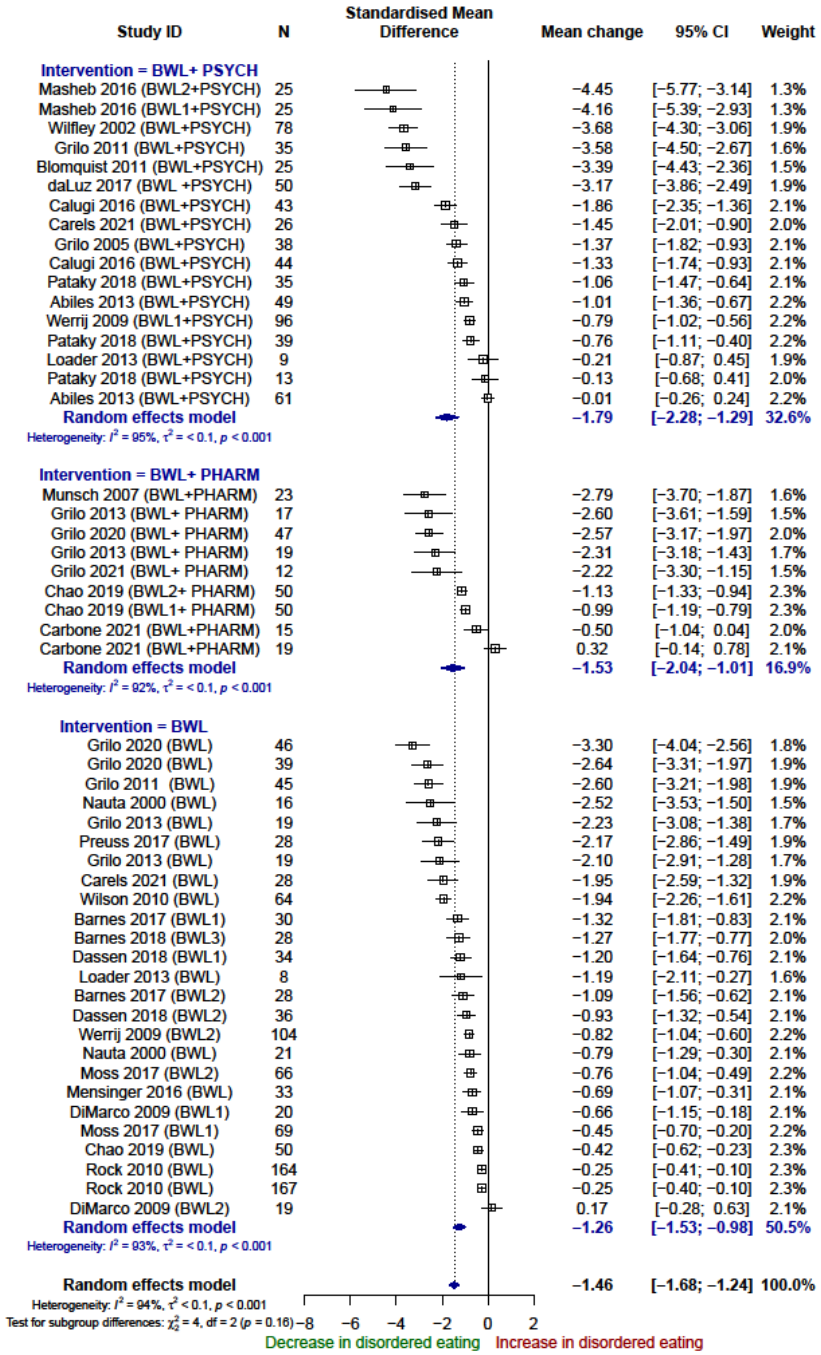
Figure 2.15. Association between weight loss interventions and disordered eating in the further follow-up, analysis of randomised control trials



2.4.4 Subgroup analyses

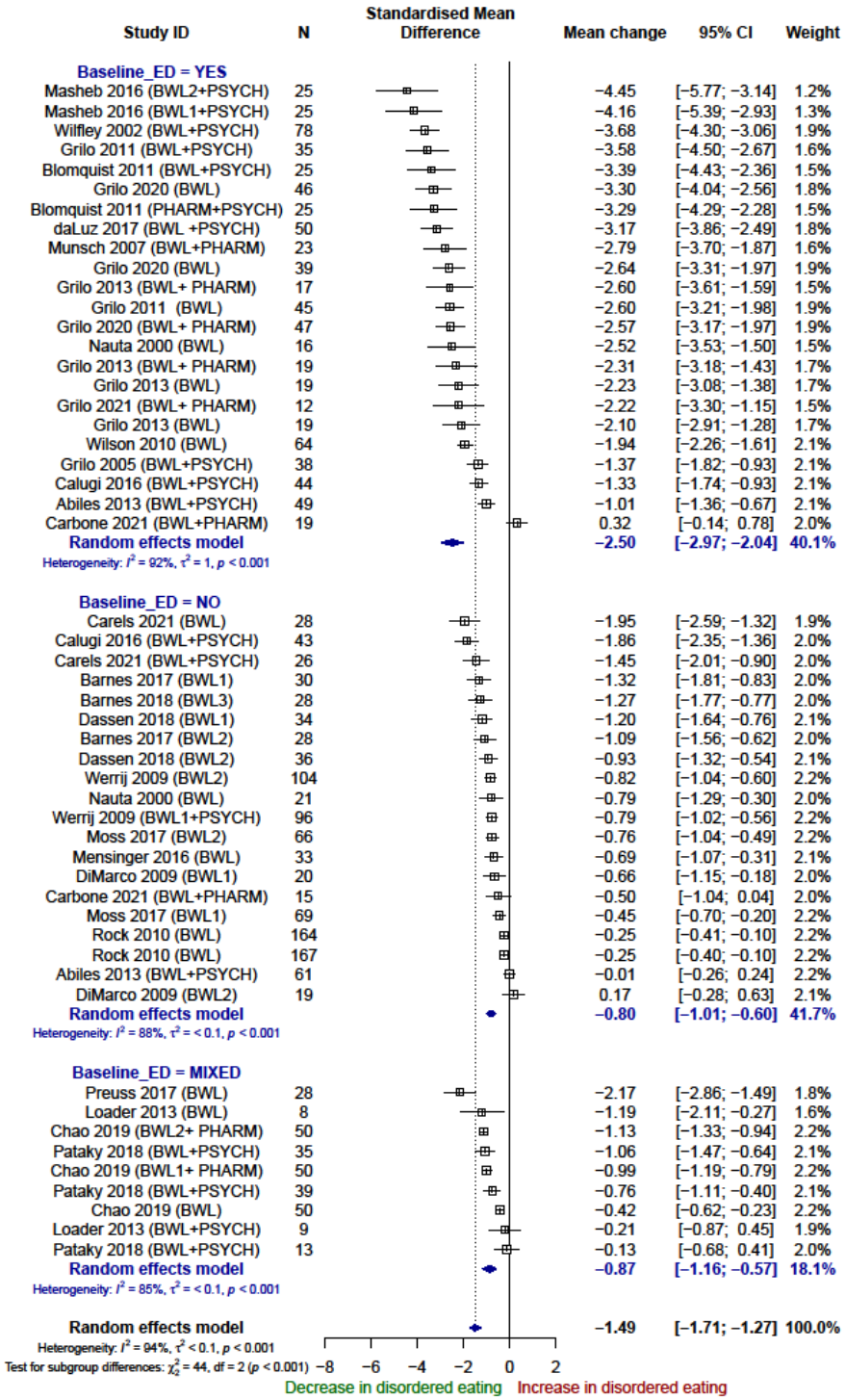
In a subgroup analysis by type of intervention, excluding the one arm combining psychological therapy and pharmacotherapy, there was no evidence of subgroup differences (p=0.16) between interventions that offered BWL alone, BWL with psychological therapy, and BWL with pharmacotherapy (Figure 2.16).

Figure 2.16. Subgroup analysis by type of intervention, pre-post analysis of single arms



In a subgroup analysis by baseline disordered eating status, there was evidence of subgroup differences ($p<0.0001$). Participants diagnosed with an eating disorder at baseline saw the largest reduction in disordered eating scores (-2.5 SMD units; 95% CI -2.97 to -2.04; I^2=92%, n=23) compared with those without disordered eating (-0.80 SMD units; 95% CI, -1.01 to -0.60; I^2=88%, n=20) or the population unselected for disordered eating (-0.87 SMD units; 95% CI, -1.16 to -0.57; I^2=85%, n=9) (Figure 2.17).

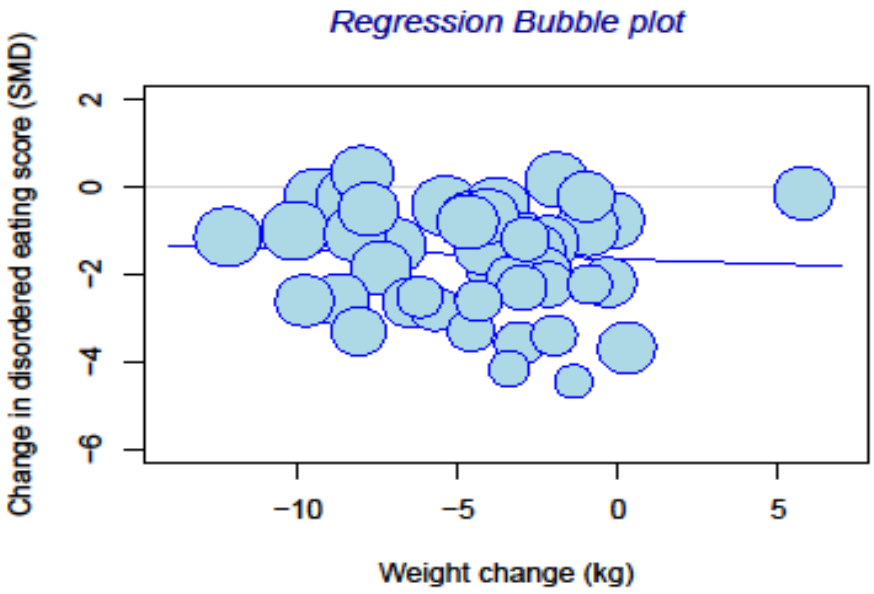
Figure 2.17. Subgroup analysis by baseline disordered eating status, pre-post analysis of single arms



In the post-hoc subgroup analysis, there was no evidence of a difference between the studies reporting EDE-Q/EDE scores directly (n=39) versus studies where scores were calculated (p=0.43) (n=13).

In the meta-regression between weight loss and disordered eating in the single-arm trials, weight loss was not associated with disordered eating change [regression coefficient -0.0228 (95% CI -0.09 to 0.05)] (Figure 2.18).

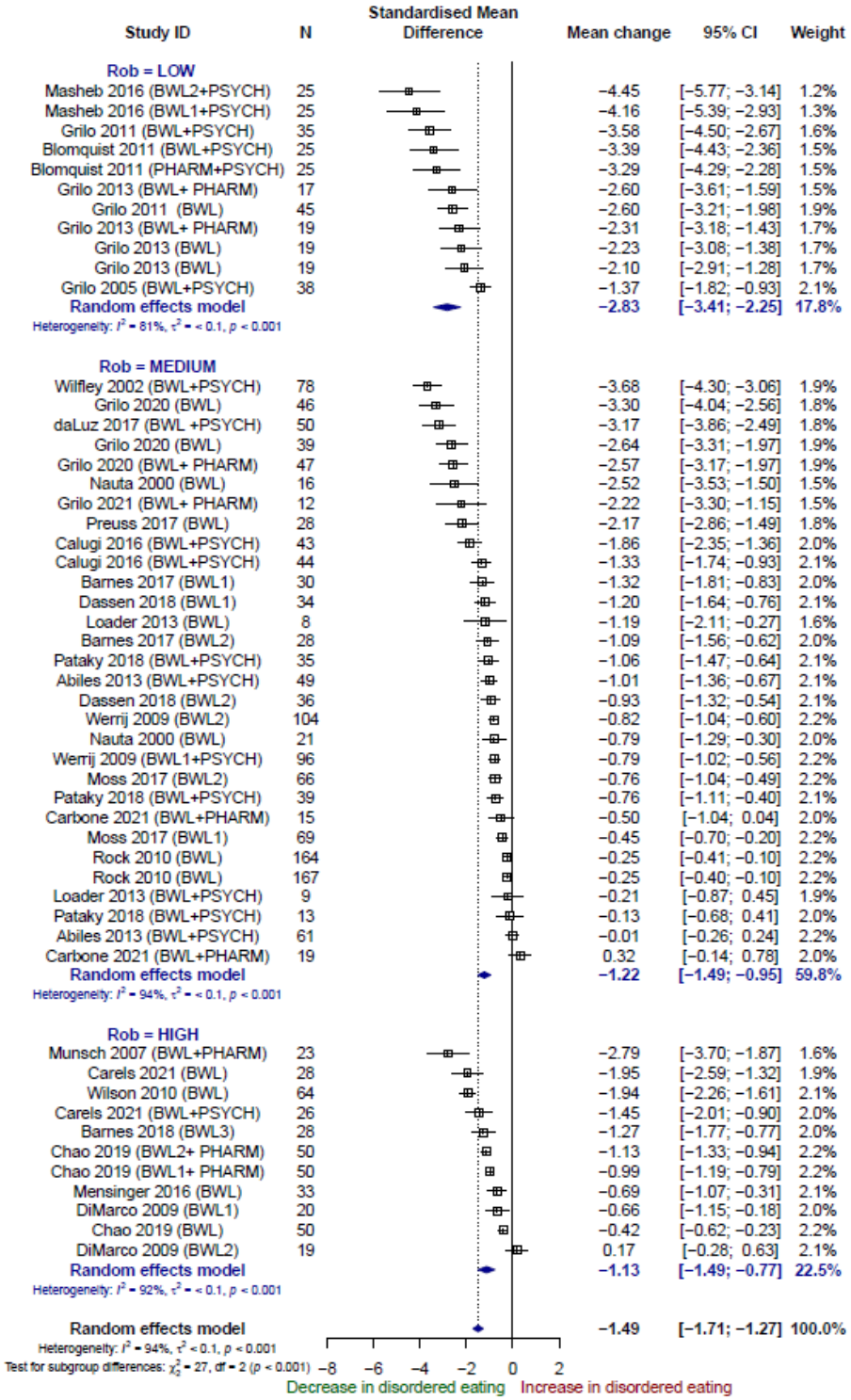
Figure 2.18. Meta-regression Bubble plot



2.4.5 Risk of bias

Eleven studies were classified as at low, 30 as at medium, and 11 as at high risk of bias. In a sensitivity analysis, there was evidence of subgroup differences by risk of bias, with studies at low risk showing larger reductions in disordered eating scores compared with studies at either medium or high risk (Figure 2.19).

Figure 2.19. Sub-group analysis by risk of bias, pre-post analysis of single arms



There was no strong evidence of publication bias based on visual inspection of the funnel plot of studies using the EDE-Q and no statistically significant asymmetry indicated by Egger's test (p= 0.0553). However, there was evidence of asymmetry in studies that assessed outcomes using the EDE (Egger's test, p= 0.0065), (Appendix A2.3, A2.4).

2.5 Discussion

In people with overweight/obesity, weight loss interventions producing modest weight loss were clearly and consistently associated with statistically significant reductions in disordered eating scores in analyses of pre-post single-arm and randomised controlled trials. This reduction in disordered eating was maintained at further follow-up and was independent of the type of intervention. The magnitude of weight loss did not predict changes in disordered eating. The reduction was larger in participants with pre-existing eating disorders than in participants without, or in participants unselected for disordered eating. Studies judged at low risk of bias showed larger effect sizes.

The Cochrane guidance was followed in conducting this review. To maximise data, I included both randomised and non-randomised trials, amounting to 31 trials with 2,730 participants from 9 countries, making it, to my knowledge, the largest review in the field. It follows syntheses of evidence of weight loss interventions on disordered eating conducted in the past without a meta-analysis[100,152] and extends the conclusions from a recent systematic review and meta-analysis[101] which excluded interventions with pharmacotherapy and did not include all trials with populations with disordered eating at baseline. By including more evidence and by calculating data needed to assess the change in EDE-Q/EDE score, the test statistic of most relevance, more precise estimates were produced, compared to previous reviews.

The effect size estimates from the single-arm analyses were larger than the effect size observed in RCTs. One explanation for this is regression to the mean. Nearly half of the trials included participants selected to have an eating disorder or disordered eating at baseline and, on average,

their scores are likely to decrease by follow-up. Trials are therefore likely to provide a better estimate of treatment effect. At treatment end, there was clear and consistent evidence of a benefit of weight loss treatment, but with only 4 RCTs the estimate at subsequent follow-up was too imprecise to conclude whether the effect was transient or persistent.

Another strength of this meta-analysis is the focus on studies that assessed disordered eating using validated tools, here EDE and EDE-Q. They are traditionally considered the "gold standard" for assessing disordered eating psychopathology and demonstrate good agreement with each other and clinical diagnoses [153]. There have been some concerns that the EDE-Q may overestimate binge eating frequency compared to EDE, which could inflate EDE-Q scores relative to the EDE. However, here change in score was calculated, which somewhat negates this concern and supports our decision to combine both measures.

There were some weaknesses in this study. There was high heterogeneity in weight loss outcomes and eating disorder symptoms. I combined different types of weight loss interventions and subgroup analysis showed no evidence of this reducing heterogeneity within these broad groups or overall. The reduction in eating disorder symptoms was greatest in people with disordered eating at baseline. Despite this heterogeneity in effect size, the direction of effect was largely consistent. Another limitation was the small number of studies included in the analysis of randomised controlled trials, meaning evidence on causality was limited. Additionally, most studies followed up participants for one year or less. Weight regain is common after programme completion[154] and future trials could investigate how weight regain and participation in multiple weight loss attempts/programmes affect disordered eating in the long term.

Another limitation is that studies of people with eating disorders included mainly people with BED. BED is commonly comorbid with overweight/obesity[60,61], and weight loss programmes may not be considered an appropriate initial treatment for people with bulimia or other eating disorders.

I excluded all studies that did not use the EDE or EDE-Q. I confined the analysis to this measure because the EDE and EDE-Q are the most widely used quantitative assessments of the core symptoms of eating disorders in the field. However, I excluded 103 studies that had other measures that relate to eating disorders, such as measures of self-esteem, or offered a less comprehensive measure of eating disorders than that provided by EDE and EDE-Q. There is no reason to believe that these studies would have systematically different results from those included. Disordered eating was measured using a continuous score not designed to diagnose eating disorders so this review can only indicate that symptoms of eating disorders decline after enrolment in a weight loss programme. Finally, the median longest follow-up was 9.5 months. Consequently, this review cannot provide evidence of the development of eating disorders in the longer term.

Participants in these programmes saw a mean rise in the restraint subscale of the assessment tools. These tools were not designed to be administered to people undergoing a BWL, during which participants are encouraged to practice dietary restraint. As such, participants following the programme by restraining their intake were expected to increase their dietary restraint scores. However, that increase observed at the end of the intervention had dissipated by follow-up. Reassuringly, all other subscales (eating, shape and weight concern) significantly reduced both at the end of the intervention and at further follow-up, which led to the reduction in the global disordered eating score. This suggests that structured support to lose weight actually helps people address these challenges.

In summary, this review showed that BWL programmes, with or without weight loss pharmacotherapy or psychological therapy, do not worsen disordered eating in people with or without eating disorders, and may even improve it.

Chapter 3. The impact of the total diet replacement programme for diabetes remission on disordered eating; a non-inferiority randomised controlled trial

3.1 Summary

In this chapter, I report the results from the ARIADNE non-inferiority randomised controlled trial, investigating the impact of a TDR programme on disordered eating scores in people living with overweight/obesity, T2D and disordered eating at baseline. I recruited 56 adults aged 18-65 years, BMI ≥27 kg/m^2, diagnosed with T2D in the last 6 years and evidence of disordered eating (global EDE-Q scores ≥2.67). They were randomised 1:1 by a blinded independent researcher, to receive the TDR programme or control (usual care). The intervention aimed to provide approximately 860 kcal/day, in the form of 4 nutritionally complete products per day, replacing all other food. The primary outcome was to assess the non-inferiority of the change in the global EDE-Q score at the end of the programme (24 weeks), compared to usual care. Secondary outcomes were non-inferiority assessment for changes in sub-scale scores of disordered eating (EDE-Q restraint, eating concern, shape concern, weight concern) and in psychosocial impairment, using the Clinical Impairment Assessment (CIA) questionnaire scores, as well as changes in weight between TDR and control arms. All questionnaires were self-reported online, however, due to lack of resources, it was not possible to blind the researcher delivering the intervention to participants' changes in scores. Non-inferiority was set at 1SD increase; SD was taken from the relevant mean scores observed in the eligible population expressing interest in the trial. Exploratory outcomes included changes in medication and changes in quality of life (measured by proxy using PHQ-9 and PAID questionnaires). A safety outcome was included to examine the safety signals of TDR in people with disordered eating, by measuring the number of participants needed to be considered for a referral to eating disorder services. Finally, the process evaluation through qualitative data analysis which was part of the trial is presented separately in Chapter 4.

Fifty-six participants were recruited using online advertisements from March to September 2023. Forty-nine of the 56 participants (87.5%) completed the study follow-up at 24 weeks. The

between-group adjusted difference in the EDE-Q score was -0.9 points (90% CI -1.3 to -0.4) at 6 months (24 weeks), indicating both non-inferiority (primary outcome) and superiority. Non-inferiority at 24 weeks was also shown for all secondary outcomes, apart from the restraint subscale, as there was no evidence that the sub-scale was non-inferior to usual care. The primary analysis was done to the intention-to-treat population, as well as the per-protocol population, with the same results. Medication for diabetes and hypertension reduced significantly in the intervention arm compared to control and quality of life increased significantly in the intervention arm, based on depressive symptoms and diabetes distress that decreased significantly. No participant was judged to be at high suspicion for having developed a new eating disorder. In conclusion, the intervention did not increase disordered eating or distress from it, with evidence that it decreased it significantly. It also improved the quality of life and reduced the number of medication participants needed. The results of the trial provide evidence that TDR can be safely offered to people who demonstrate disordered eating.

Note: The protocol for this study has been published in the Contemporary Clinical Trials journal[155].

3.2 Introduction

As discussed in Chapter 1, the DiRECT[156] and DROPLET[157] studies paved the way for the pilot NHS Path to Remission programme, offering TDR to people living with T2D and overweight/obesity in September 2020, and the early uptake and outcomes have just been published[158]. However, given the high prevalence of people with T2D often experiencing disordered eating symptoms, the programme was met with concern from some groups, in particular eating disorder charities and some healthcare professionals, who considered that the restrictive nature of the treatment may exacerbate disordered eating behaviours.

There has been more and more discussions in the public sphere around “diet culture” recently and the impact of weight loss on the risk of developing disordered eating[106], the prevalence of

which is increasing[159] in recent years, sometimes with devastating consequences[58]. Healthcare professionals are often hesitant to recommend rigid regimens, such as TDRs, to patients, partly due to safety concerns on their potential negative psychological impact[105], and anecdotally, due to fears that these regimes could trigger eating disorders. Indeed, TDR programmes incorporate rigid rules around eating, severe energy restriction, and concentration on monitoring weight. Theories hypothesising that dieting and caloric restriction could cause eating disorders formed as early as 50 years ago[160]. More recent research showed that restraint, the cognitive effort to control one's food intake to control their body weight, could cause overeating and potentially eating disorders[161], whereas monitoring weight has been positively associated with eating disorder symptomology[162].

The NHS Path to Remission programme has been available since the 1st of April 2024 to all people meeting eligibility criteria residing in England. There might be a significant proportion of healthcare professionals who are hesitant to refer their participants or actively encourage against such approaches to weight loss. Furthermore, there have been discussions and active advocacy from some stakeholders for screening for eating disorders before referring to the programme. At present, only people with an active diagnosed eating disorder are excluded. Any implementation of screening will inevitably increase the use of healthcare time, either at GP level or at provider level, leading to higher costs and excluding participants who could otherwise benefit from diabetes remission and weight loss. No tool is robust enough to be used for this purpose. The EDE-Q which is derived from the gold standard assessment interview of EDE is a research tool which is lengthy and can measure risk for high eating disorder psychopathology. The EDE was originally developed as a research outcome measure to be used in studies on women[163], however, the EDE-Q cannot be used to diagnose an eating disorder. Other tools have been developed but they measure either only some aspects of disordered eating (e.g. binge eating score, BES[164] or emotional eating scale[165]) or have high sensitivity with potentially low specificity when used in people living with obesity/overweight and/or dieting (e.g. SCOFF questionnaire[166]), thus being not

fit for purpose. Using a sub-optimal tool until there is a better one would only be justified by high concerns that the programme can actually be harmful.

The current study aimed to assess the potential of such harm: whether people living with overweight/obesity and T2D who have a high risk for developing an eating disorder based on high EDE-Q scores at baseline, undergoing a programme identical to the NHS Path to Remission programme will experience a deterioration in their eating behaviour to a greater extent than those undergoing usual care. Other objectives included assessing non-inferiority for clinical impairment caused by disordered eating, exploring changes in medication and quality of life and diabetes distress between arms and evaluating the process of change, by attempting to understand experiences, barriers, facilitators, and changes in eating behaviour and disordered eating symptoms, using qualitative analysis (presented in Chapter 4).

3.3 Methods

3.3.1 Study design, participants, and recruitment

This was a prospectively registered, pragmatic, non-inferiority, parallel, individually randomised controlled trial. It examined the impact of a programme resembling the NHS Path to Remission programme on disordered eating in susceptible individuals living with overweight/obesity and T2D. As a result, the chosen eligibility criteria mirrored the criteria for enrolment in the NHS pilot of T2D remission with the addition of criteria for disordered eating[167]. I defined a score ≥2.67 as indicating disordered eating, as proposed by Mond and colleagues in 2008 [120] for an "older" population, given the risk of T2D increases with age[168]. In addition, people living with overweight/obesity tend to score higher than people with a healthy BMI. In a Norwegian study, BMI significantly correlated with the global EDE-Q score, as participants with obesity (BMI ≥ 30 kg/m^2) reported a score around 2.3 times greater than people without obesity[169]. All inclusion and exclusion criteria are presented in Table 3.1.

The study aimed to show whether the programme is safe for people at risk of an eating disorder by virtue of having disordered eating at enrolment. People with a suspected and/or diagnosed eating disorder were excluded from the programme, following existing NHS guidelines. To mitigate the risk of enrolling people with undiagnosed eating disorders, people with an EDE-Q≥4 and a CIA score ≥16 were excluded.

The duration of participation was 2 years, with the primary outcome assessed at the end of the intervention, which was 6 months. The protocol was reviewed and approved by the Medical Sciences Interdivisional Research Ethics committee (CUREC 3) and was prospectively registered (NCT05744232, ClinicalTrials.gov), as well as published following peer review[155]. There is also scope for expanding recruitment using NHS resources kindly offered by NHS England, therefore the study expansion was reviewed and approved by the Camberwell and St Giles Research ethics committee (REC reference: 23/LO/0633).

To recruit participants, online advertisements for the study were used, calling potentially eligible participants to read the study patient information sheet (PIS), have a phone call with me if they have any questions about the study, and then fill in an online, self-reported eligibility survey which took around 30-40 minutes. The advertisements were placed on the Diabetes UK forum (https://forum.diabetes.org.uk/boards/) once and on social media (Google adverts and Facebook adverts). To do the latter, I utilised the services of Health Research, a digital marketing company connecting interested participants with relevant research studies (https://www.healthresearch.study/). The service does not have access to any participant information and all resources used to advertise were made available to ethics for approval. If people living with T2D find out about their study through existing trial participants, they could self-refer to the trial by contacting the study team who directed them to the screening process.

Advertisement online was deemed as the most efficient way to recruit people with disordered eating and T2D; the advert could reach a larger sample in a small amount of time, compared to participants attending their practice and responding to a poster or a member of the study team

speaking to them about the study. This way, it was also deemed to have a smaller impact on busy GP practices and to be more time efficient[170]. The study also ran during the pilot expansion of the NHS Path to Remission in England[39]; as a result, the need was to recruit from all areas where the programme was not available as part of the pilot to avoid cross-contamination of the control group, if they were enrolled in the NHS Path to Remission programme while randomised to control in the study. As a result, the company promoted the study in all England, excluding the following areas where the programme was available: Nottingham and Nottinghamshire (inc. Bassetlaw), Lancashire and South Cumbria, North East and North Cumbria, Somerset, Birmingham and Solihull, Humber and North Yorkshire, Gloucestershire, Bedfordshire, Luton and Milton Keynes, Black Country, Mid and South Essex, South West London, South Yorkshire, Greater Manchester, Frimley, Derbyshire, North East London, North Central London, West Yorkshire, Kent and Medway, Sussex, Bristol, North Somerset and South Gloucestershire Integrated Care Boards (ICBs).

Remote screening assessment also sped up the process of recruitment and minimised resources needed, and therefore cost.

The eligibility survey included questions on all eligibility criteria as well as four questionnaires (EDE-Q, CIA, PHQ-9, PAID; their score is outlined below in section 3.3.4). At every page, if a participant selected a response deeming them ineligible, then the survey would conclude and they were screened out. Some questions asking for medical history had an option of "unsure", to enable the participant to proceed with the survey, as there was an opportunity to clarify the answer in the eligibility phone call which would follow. Data were recorded directly onto the case report form (CRF) by participants into REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Oxford on a secure server.[171] REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical

packages; and 4) procedures for importing data from external sources. The system has an inbuilt audit trail facility and the ability to run internal validation checks. Entries are embedded with mandatory fields are required and range checks in order to minimise the risk of missing data and data queries.

Table 3.1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Willing and able to give informed consent and can communicate in English • Age 18-65 years • Resident in England • BMI ≥27 kg/m^2 (≥25 kg/m^2 for people of Black, Asian and minority ethnic origin) • Diagnosed with T2D within 6 years prior to the day of screening • Global EDE-Q scores ≥2.67 • HbA_{1c} ≥43 mmol/mol (6.1%) and ≤87 mmol/mol (10.1%) if on diabetes medication OR latest hbA_{1c} ≥ 48 mmol/mol (6.5%) and ≤87 mmol/mol (10.1%), if not on diabetes medication, done within the last 12 months • If diagnosed with type 2 diabetes more than 1 year from day of screening, the participant must have attended their GP surgery for monitoring/ diabetes review when last offered • Commit to continue annual reviews with their GP, even if T2D remission is achieved	• Self-reported current or previous clinical diagnosis of an eating disorder • Combination of EDE-Q ≥4 AND CIA score ≥16 at screening • Currently participating in a structured weight loss programme or self-reporting weight loss of >10% in the last 3 months • Insulin use • Known kidney disease of stage 3/4/5 or eGFR <60 mls/min/1.73 m2 within the last 12 months • Active substance use disorder • Porphyria or active liver disease (not including non-alcoholic fatty liver disease) • Known proliferative retinopathy that has not been treated • Undergone or awaiting bariatric surgery • Myocardial infarction or stroke within the previous 6 months • Severe heart failure (New York Heart Association grade 3 or 4) • Pregnant, breastfeeding, or planning to become pregnant during the course of the study • Soy or fish or milk allergy, lactose intolerance, or following a vegan diet • Active cancer other than skin cancer

3.3.1.1 Patient and Public Involvement (PPI)

I involved the public from the stages of conceptualisation of this work and applying for funding. In December 2020, I had 1:1 sessions with five people with diabetes, obesity, and a previous attempt to lose weight. We discussed weight, body image, dieting and diabetes remission. They all welcomed the proposal giving feedback that they considered it an essential piece of work to shed some light on this important issue. In particular, two participants had gone through total diet

replacement for diabetes remission and obesity and found some disordered eating behaviours related to binge eating and obsession with food aggravated after that. They both related this to previous, baseline disordered eating behaviours and not having the support needed (as they went for TDR privately/on their own, without the behavioural support the programme offers but solely buying the products). Therefore, they thought this programme would need to mimic the way it will be delivered in the NHS, with the appropriate support and follow-ups, to see if this makes a difference. Another participant also highlighted the need for support, regular follow-ups and problem-solving techniques, to support people from different cultural backgrounds who might find compliance to the diet a challenge, which could then affect their mental health.

Two other participants who had successfully lost weight following other methods wished their GP had offered them a low-energy behavioural weight loss programme to reverse their diabetes when diagnosed. Some pursued weight loss programmes privately and reported feeling a lot better after having gone through it. They all expressed how difficult it felt in the beginning but how this feeling changed gradually by adhering to the programme. They mentioned the importance of family and peer support and they also kindly suggested ways of boosting recruitment and facilitating attendance to study visits. They did not report any issues in terms of disordered eating, thinking of food, and body image.

Throughout my DPhil, my PPI panel expanded. As the NHS pilot expanded in England, more and more people became familiar with the intervention. People were keen to bring a patient perspective to the discussion of recruiting and conducting the trial, addressing challenges such as adherence retention, and interpreting the results. As a result, I further consulted a group of four people living with obesity and diabetes and one carer in the first year of my DPhil while preparing my application for study ethical approval. They were a mix of people I previously consulted and new PPI contributors; they offered invaluable input in designing the advert for study recruitment,

study materials, the support offered, as well as wording in the protocol and study materials of concepts challenging for lay language, like disordered eating.

I plan to disseminate the results of the study to both participants and PPI contributors alike, in a lay language brief when the study ends.

3.3.2 Study procedures, randomisation and blinding

After a survey response was completed, I emailed an invitation to potentially eligible participants to arrange a phone call and clarify eligibility. During the phone call, I answered participants' questions and clarified whether each participant was eligible. If there was uncertainty, with the participant's consent, I would contact their GP for clarifications via secure nhs.net email. I emailed the study GP and supervisor, Dr Aveyard, to confirm eligibility of participants. Finally, only when participants were confirmed to be eligible and happy to be randomised, I proceeded with randomisation. Participants were randomised to one of the two study arms using a minimisation software (MinimPy[172]) with a 20% random element balancing gender (man/non-binary/other or woman) and EDE-Q global score (≥3.9 and <3.9). The 3.9 cut-off for EDE-Q was chosen based on previously reported means of EDE-Q scores on populations with obesity and subclinical disordered eating[173,174]. Randomisation was conducted by my supervisor, Dr Koutoukidis, blinded to baseline data who then would inform me to notify the participant about their allocation. Due to the nature of the intervention, it was not possible to blind participants or the clinician delivering the intervention. However, the assessment of the primary outcome was blinded, as questionnaires were self-administered online.

3.3.3 Sample size

The process of sample calculation involved taking two different approaches to ensure robustness, in the absence of clear evidence in the literature. The Sealed Envelope online calculator for continuous outcomes in non-inferiority trials[175] was used in both approaches.

1st approach: In a study where community EDE-Q scores were measured in people without a diagnosis of an ED, people with obesity scored a mean of 2.75 on global EDE-Q score[174], with an

SD of 0.97, which is close to the SD observed in people with normal BMI (SD=0.86) in the same study. If the majority of people living with obesity score around 2.75 (mean), we want at least the majority not to reach the cut-off of 4, after which there is a high risk for the presence of an eating disorder. Defining the non-inferiority limit d, a maximum difference we could allow as non-inferior would be this of the difference between the mean 2.75 and the set cut-off of 4 where concerns arise (d=1.25). If there is truly no difference between the standard care and TDR, then 28 participants are required (n=14 per group) to be 95% sure that the upper limit of a 90% two-sided confidence interval will be below the non-inferiority limit of +1.25. Accounting for a 10% dropout[27], 32 participants (n=16 per group) are needed.

2nd approach: When EDE-Q is used as an outcome in studies investigating the effectiveness of different ED treatments, a post-treatment score less than 1 SD above the community mean is considered meaningful[176-178]. If the maximum change allowed for non-inferiority would be a change of EDE-Q global score equivalent to 1 SD from the population mean, then 44 people (n=22 per group) were needed to be 95% sure that the lower limit of a two-sided 90% confidence interval would be below the non-inferiority limit of +1 SD. In discussion with clinicians, academics, and a statistician, one SD was confirmed as the minimum clinically meaningful increase, based on their feedback. Accounting for a 10% dropout, 50 participants (n=25 per group) are needed. Given the study population has disordered eating already, there might be a higher risk for drop-out; accounting for a generous 25% dropout, 56 participants (n=28 per group) are needed. This was deemed as a rigorous scientifically but also achievable goal for recruitment in the context of the DPhil.

Depending on each population, the SD can vary; in a study that investigated the impact of a coached online intervention for sub-clinical disordered eating (excluding people with a diagnosis of an ED) on disordered eating symptomatology, the standard deviation of the EDE-Q score was 0.9 pre and 0.7 post intervention[179]. Since there are no previous studies on this population of

people with overweight/obesity, T2D and disordered eating, the mean score and SD of the population who successfully completed the eligibility screening but did not proceed to randomisation was used in this case.

Table 3.2 Sample size calculation scenarios

Non-inferiority limit, d	SD of outcome	Study derived	Significance level (α)	Power (1-β)	Sample size (n per group)	Sample size after % attrition
0.97	0.97	Aardoom et al., 2012[174]	5%	95%	44 (n=22)	50 (n=25), 14%
1SD (e.g. 0.97)	1 SD (e.g. 0.97)	Aardoom et al., 2012[174]	5%	95%	44 (n=22)	56 (n=28), 25%
½ SD (0.485)	1 SD (0.97)	Aardoom et al., 2012[174]	5%	90%	138 (n=69)	154 (n=77), 10%
½ SD (0.485)	1 SD (0.97)	Aardoom et al., 2012[174]	5%	95%	174 (n=87)	192 (n=96), 10%
½ SD (0.485)	1 SD (0.97)	Aardoom et al., 2012[174]	5%	95%	174 (n=87)	218 (n=109), 25%

Figure 3.1 Visual representation of non-inferiority conditions

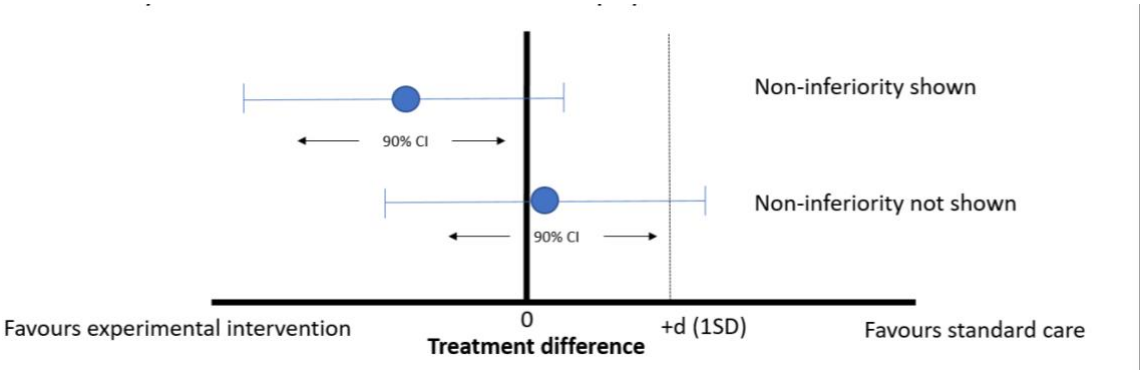
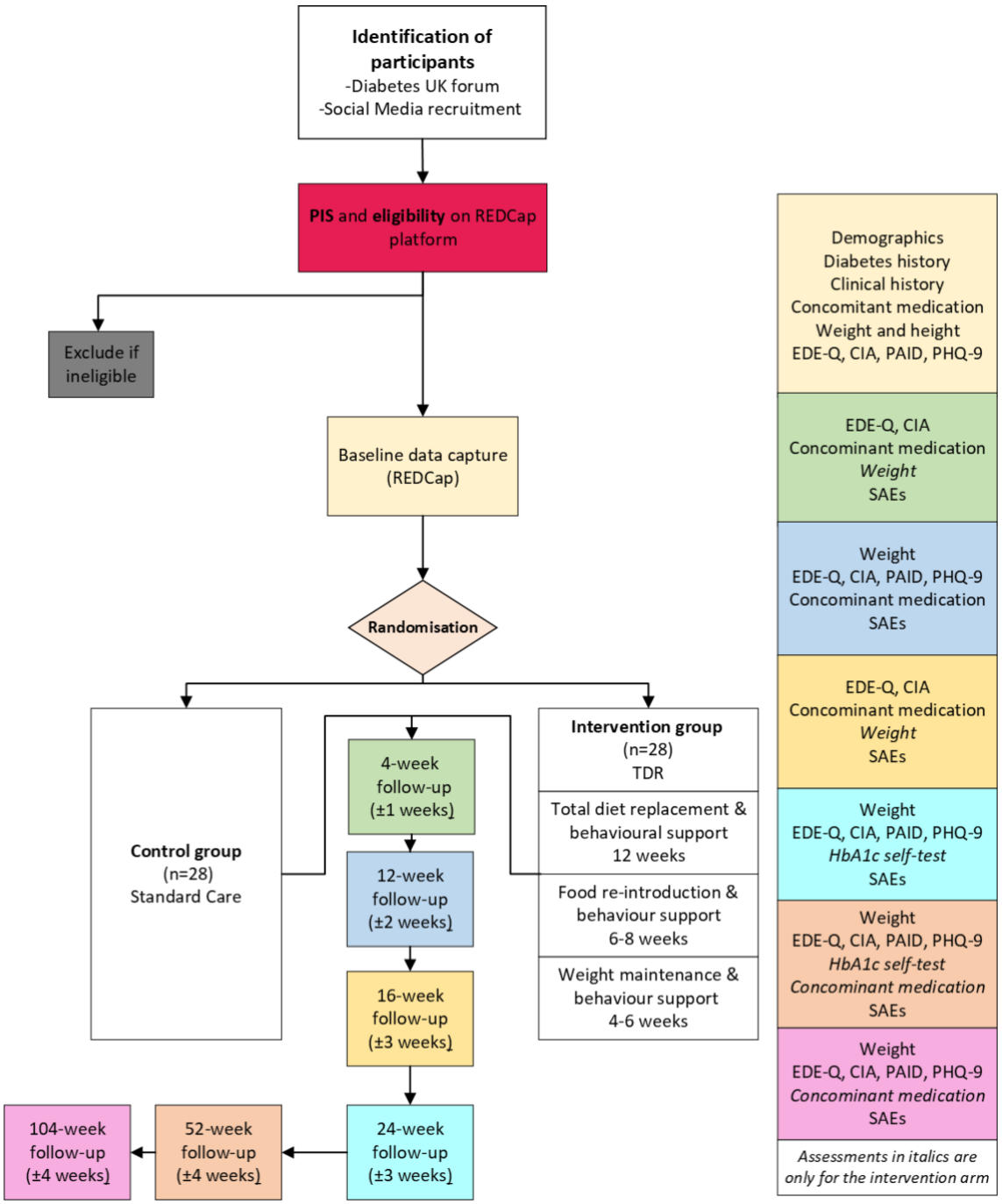


Figure 3.2 Study processes



3.3.4 Intervention and control

3.3.4.1 Intervention

The aim was for participants in the intervention arm to start the programme as soon as possible after randomisation. This was to minimise significant changes in weight compared with the one reported at baseline. During the intervention, intervention adherence, blood glucose, and blood pressure were assessed (methods described below). Participants in the intervention group were offered a dietitian-delivered intervention over 6 months, similar to the NHS pilot of low-calorie diets for type 2 diabetes remission[39]. I delivered the programme to all participants in the intervention arm. The intervention started with 12 weeks of low-energy total diet replacement (approx. 860 kcal/day) in a nutritionally complete package of soups, shakes, and bars. I usually asked participants the flavours they preferred and sent them a first package of various products to try. Once I established preferences after trialling the products, I would order their preferred products at regular intervals. It continued with stepped food reintroduction (maximum 6 weeks)

as a low-calorie, nutrient-rich diet personalised to the individual participant's circumstances and preferences, and weight maintenance (4-6 weeks).

Breakdown of the intervention

1. **Weeks 1-12 (TDR phase)**: The first session was around 45 minutes long and the rest of the sessions were around 15-30 minutes long delivered over the phone. They occurred approximately at Week 0, 1, 2, 4, 6, 8, 10 and 12, but this was modified according to participants' needs/availability and the dietitian's judgement. Participants were encouraged to consume 4 formula products per day. There was an allowance of up to 100 ml of skimmed milk (for coffee, tea etc.), if needed. During the sessions at week 10 and 12, I started discussing the food reintroduction phase.
2. **Weeks 13-14 (Food reintroduction phase I):** This session was approximately 30 minutes long. Participants were advised to consume 3 formula products per day with an allowance of up to 100 ml of skimmed milk (for coffee, tea etc.), if needed. They were also advised to consume a small high-protein, low-carbohydrate, low-fat meal (approximately 200 kcal), unlimited salad/non-starchy vegetables and one portion of fruit.
3. **Weeks 15-16 (Food reintroduction phase II):** This single session was around 15-30 minutes. Participants were advised to consume 2 formula products per day. They were also advised to consume a lunch based on a small high-protein, low-carbohydrate, low-fat meal, unlimited non-starchy vegetables (e.g. made into a salad or soup), 2 portions of fruit, and ~400 kcal evening meal based on the healthy eating guidance.
4. **Weeks 17 till 20 (Food reintroduction phase III):** These sessions on weeks 17 and 19 were 15-30 minutes long. Participants were advised to consume one formula product, plus meals to continue weight loss or maintenance according to participant preference. At this stage, I started discussing physical activity and mild exercise was recommended,

according to what the participant used to do before the programme and was able to now incorporate into their day-to-day life.

5. **Weeks 21 till 24 (Maintenance phase):** The sessions on weeks 21, 23, and 24 were 15-30 minutes long. Participants were advised to consume regular food based on the healthy eating guidance in quantities to aid weight loss maintenance. There was a provision for an optional small treat (up to 300 kcal) a week. The standard UK Chief Medical Officers' Guidelines on physical activity were also discussed: at least 150 minutes of moderate-intensity activity, 75 minutes of vigorous activity, or a mixture of both, strengthening activities on two days and reducing extended periods of sitting.

The intent was for participants who missed sessions due to illness, holidays, or other reasons to be offered an extended next appointment, so that the total intervention time remained constant, as much as possible. However, sessions were led by participant availability and enquiries/needs, therefore there were minor differences between dietetic time spent with each participant.

During the beginning and until the food reintroduction phase II, participants were recommended to take a daily fibre supplement. This was provided for free (Fyrogel, ispaghula husk). During the food reintroduction phase, I discussed examples of meals, cooking methods, and recipes with participants. Throughout the whole programme, participants were encouraged to drink at least 2.5 L of energy-free fluids per day.

Participants in the intervention group were asked to monitor their capillary blood glucose and blood pressure at home using a glucometer and a blood pressure monitor. These were provided with the manufacturer's guide on how to use the devices appropriately and were also signposted to the Diabetes UK video on "How to test your blood sugar levels- 7 simple steps" and the British Heart Foundation's video on "How to measure your blood pressure at home", respectively. When on TDR (first 12-week phase) they were advised to measure at least weekly in weeks 1-4 and at least every 2 weeks in weeks 5-12. When not on TDR (post week 12), they were advised to

measure at least monthly. They were prompted to make a note of each reading to communicate this to me during the intervention call. This was a safety measure to allow for medication adjustments if necessary. If participants didn't provide any readings for the first four weeks of the TDR phase or any readings for any 8 weeks in a row they had to be discontinued from the intervention. Reminders to measure blood glucose and blood pressure were offered during dietetic sessions; reasons for difficulties with adherence were explored and solutions were offered.

I developed two booklets to help participants navigate the programme, one for the TDR and one for the food re-introduction phase; I used publicly available resources by commissioned commercial providers to reflect their content. The behavioural content and more information on the intervention, as well as the booklets, can be found in the Appendix 3. Participants were not prevented from using any additional form of weight management support and any actions were recorded at research visits.

3.3.4.2 Control

Participants allocated to the control group continued receiving standard care. Participants were not discouraged from pursuing any behavioural weight management programme and this was recorded at 6 months.

3.3.5 Outcomes

3.3.5.1 Primary outcome

The primary outcome of this study was the change in the global score of the self-administered EDE-Q measured at 6 months. The EDE-Q [180] was used to measure disordered eating. EDE-Q is a 28-item self-report questionnaire that measures the frequency and severity of thoughts, emotions, and behaviours characteristic of the psychopathology of disordered eating. It consists of 4 subscales; restraint, eating concern, shape concern, and weight concern. Scores are calculated for each subscale and added to create a global score; higher scores on both the subscales and the global scale indicate more disordered eating behaviours and attitudes. It was

developed based on the Eating Disorder Examination Interview (EDE-I), which is considered the instrument of choice in the assessment and diagnosis of eating disorders based on the DSM-V criteria[181]. The EDE-Q demonstrates acceptable internal consistency for its subscales in various studies[182-184], with Cronbach's α mostly ranging from 0.74 for Restraint to 0.93 for Shape concern. It was also selected for its high test re-test reliability in both the 4 subscale scores and the global score[182,185], given it was intended to be administered during multiple consecutive follow-ups. It also has to be completed by participants, reducing the burden of assessment on the trial team. It was hence selected as the primary outcome.

Table 3.3 Secondary, exploratory and process evaluation outcomes in the ARIADNE study

	Outcomes	**Assessment time point(s)**
Secondary	Non-inferiority assessment for changes in sub-scale scores of disordered eating (EDE-Q restraint, eating concern, shape concern, weight concern)	Baseline, 4, 12, 16, 24, 52 and 104 weeks
	Non-inferiority assessment for changes in psychosocial impairment (CIA questionnaire scores)	Baseline, 4, 12, 16, 24, 52 and 104 weeks
	Changes in weight between TDR and control	Baseline, 12, 24, 52 and 104 weeks
Exploratory	Changes in medication	Baseline, 12, 24, 52 and 104 weeks
	Changes in depression and diabetes distress (measured using PHQ-9 and PAID questionnaires)	Baseline, 12, 24, 52 and 104 weeks
Process evaluation	Qualitative analysis of experiences, barriers, facilitators, and changes in eating behaviour and disordered eating symptoms, to understand process of change	Throughout the study

Safety	Examine the safety signals of TDR in people with disordered eating, by determining the incidence of cases of high suspicion of a new eating disorder, measured by referral of participant to see their GP for further referral to specialist services	Throughout the intervention

3.3.5.2 Secondary, exploratory and process evaluation outcomes

Secondary outcomes for this study were: change in the subscale scores of EDE-Q (restraint, eating concern, shape concern, weight concern) measured at 6 months and change in psychosocial impairment, (using between-group changes in the self-administered CIA questionnaire scores measured at 6 months.) The CIA score[186] measures the severity of psychosocial impairment associated with disordered eating. It is a 16-item self-report measure which has been developed to assess functional impairment in various domains of life and is used to compliment the EDE-Q questionnaire scores. Scores range from 0 to 48, with higher scores indicating more significant impairment. Finally, another secondary outcome was change in self-measured weight between intervention and control at 3, 6, 12 and 24 months. These time-points signify the main milestones of the TDR programme at 3 months with the transition from TDR to food re-introduction and then the end of the programme at 6 months. Weight was self-reported with a home measurement. Participants receive instructions on measuring their weight in a standardised manner (e.g., light clothing, early morning).

Exploratory outcomes for this study included change in the number of diabetes medications between baseline and 6, 12 and 24 months and change in diabetes distress and depression symptoms, used as a proxy of quality of life, between TDR and control, measured by the PAID and PHQ-9 questionnaires, at 3, 6, 12 and 24 months. The Problem Areas in Diabetes score (PAID),[187] a 20-item self-administered questionnaire, was used as a diabetes-specific quality of life questionnaire, identifying the areas of distress in living with diabetes. Total scores of 40 and above indicate severe diabetes distress[188]. PAID has excellent internal reliability with a Cronbach's α of 0.96[187]. Diabetes distress has been associated, amongst others, with ineffective strategies in

coping with stress like emotional eating[189], and was therefore deemed important to include, especially when remission is a goal of the TDR programme. The Patient Health questionnaire (PHQ-9)[190] is a 9-item self-administered questionnaire that measures symptoms of depression, reflecting the DSM-5 criteria. Scores range from 0 to 27, with higher scores indicating more severe depressive symptoms. Scores of 5, 10, 15, and 20 represent cut-points for mild, moderate, moderately severe and severe depression, respectively. It is quite brief to be administered, validated (Cronbach's α= 0.86 in primary care[190]) and widely used in primary care, as indicated by the National Institute for Health and Care Excellence (NICE)[191]. Depression and distress in T2D might overlap, but are distinct concepts; it was therefore important to be explored alongside, using these two questionnaires.

The safety objective was measured by the number of referrals of participants to see their GP for further referral to specialist services throughout the programme, deemed by me, the study dietitian, after discussing with supervisors and the study DMEC at regular intervals.

3.3.6 Measurements

A schedule of measurements can be found in the Table 3.4 below.

Table 3.4 Schedule of study measurements

	Week -2	Week 0	Week 4 (±1 week)	Week 12 (±2 weeks)	Week 16 (±2 weeks)	Week 24 (±3 weeks)	Week 52 (±4 weeks)	Week 104 (±4 weeks)
	Screening		Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6
Posting scales	x							
Confirming with GP if eligible, in case participant unsure about certain answers	x							
Informed consent	x							
Demographics	X*							
Diabetes history	X*							
Concomitant medication	X*		x	x	x	x	x	x
Self-weighing		x*	x#	x	x#	x	x	x
Self-reported height	X*							
EDE-Q, CIA	X*		x	x	x	x	x	x
PAID, PHQ-9	X*			x		x	x	x
HbA_{1c} (home-kit)						x#		
Adverse event assessments			x	x	x	x	x	x
**Data retained only if eligible, #only for participants in the intervention arm*								

3.3.6.1 Baseline assessments

If participants were deemed eligible and randomised, baseline data was retained as their baseline assessment. If needed, some questions were confirmed with the participant over the phone.

3.3.6.1.1 Demographic and clinical questionnaire

Demographic characteristics including participant's full address and postcode, date of birth, sex, ethnicity, year of T2D diagnosis, last HbA_{1c}, past medical history were collected. First & last name, full address, date of birth, GP details were collected as necessary for any contact with the participant's GP, to communicate important information for safety and handover at the end of

the study, as well as to post TDR products, blood pressure and glucose monitors, and HbA_{1c} self-test home kits. GP practices also require full name, date of birth and postcode in communications to ensure the right patient has been identified. The postcode was converted to an index of multiple deprivation and used in baseline demographics. Medication information was required for safe manipulation throughout the study.

3.3.6.1.2 Baseline weight and height

Weight and height were self-reported during screening, but weight was necessary to be based on a measured value before randomisation, either using participants' own scales or scales provided by the research team. If weight and height were recorded in stones/pounds and feet/inches as per participant's preference, these were converted to kilograms and metres (1 stone=6.3503 kg, 1 pound=0.4536 kg, 1 foot= 0.305 metre, 1 inch=0.0254 metre).

3.4.5.1.3 Prescribed medication

Participants were asked if they take any prescribed medication and if they did, they were prompted to upload a picture of their prescription or medications on REDCap at screening, to establish eligibility and to ensure safe manipulation, if needed, after randomisation. There was also an option to upload these at a later time or to discuss baseline medication over the phone. For participants randomised to the intervention, the study GP advised on medication adjustments as necessary during the trial to ensure patient safety in line with the NHS pilot medication adjustment guidance. Participants' GPs were informed of the adjustments, were sent a link to the NHS protocol for managing medication and were given the opportunity to speak to the study team. There was a question on each follow-up for the control group, as to whether there had been any changes to participant's medication; if the answer "yes" was selected, the survey asked them to upload a picture of their prescription or medications and/or describe these changes. For the intervention group, since there were regular calls with the study dietitian for delivery of the programme, the medication changes were recorded during this call.

3.3.6.1.4 Questionnaires

Participants completed the electronic versions of the EDE-Q[180], CIA[186], PHQ-9[190] and PAID[187]. The answers during the screening process were regarded as their baseline assessment.

3.3.6.2 Subsequent assessments

3.3.6.2.1 Intervention adherence

Adherence to the programme was monitored by self-report and weight loss (with non-adherence defined as weight loss of <5% at 24 weeks compared to baseline) during intervention delivery and throughout the programme. This was required as part of the intervention to facilitate problem-solving for participants who encountered difficulties with the programme to support them in overcoming them. For the control group, self-reported use of TDR at 6 months was determined as non-adherence to usual care, by means of answering the question "Have you followed any weight management method during the last 6 months?". If they replied yes, then participants were asked to fill in a box to "please describe, in little detail, the weight management method pursued?" (E.g. name, who was delivered by, where, was it private or on the NHS etc.).

3.3.6.2.2 Self-weighing

During follow-ups, participants in both groups were asked to weigh themselves in the morning right after waking up, in light clothes and with an empty bladder. Participants who did not have a scale at home were provided with one at the eligibility stage. Participants were asked to insert the weight value on the REDCap follow-up link at each follow-up time point. Participants in the intervention group had to measure their weight more often during the intervention and communicated this to the study dietitian in order to re-assess goals at each point, however specifically for the follow-ups, they had to insert it on REDCap.

3.3.6.2.3 Questionnaires

Participants completed the electronic versions of a combination of EDE-Q, CIA[186], PHQ-9[190] and PAID[187], depending on the follow-up time point. EDE-Q and CIA were assessed on every follow-up, to determine whether there is a trajectory in the disordered eating scores and its impairment. There was a particular interest in adding a follow-up at 4 weeks, to capture how participants did after a month on TDR and then at 16 weeks, one month into food reintroduction, where it was

anticipated participants might experience challenges, as previously documented in relevant qualitative research[192]. The primary outcome was at 6 months, which is the end of the programme and would offer evidence on the impact of the programme short-term. Depressive symptomatology and diabetes distress were deemed important to be assessed, however, I aimed to reduce the burden on participants by asking participants to record the PHQ-9 and PAID at 12 and 24 weeks only during the programme.

Longer-term follow-ups at 12 and 24 months were selected to assess long-term outcomes, similar to other studies on TDR and T2D remission in the field[31,103].

3.3.6.2.4 Blood sample home kit (HbA1c)

Intervention participants were offered a self-assessment kit to assess their HbA_{1c} at 24 weeks. This was done to assess the effect of the intervention on diabetes and whether medication had to be re-introduced, in order to safely handover participants' care back to their GP. The kits were registered to the provider's website prior to being sent to the participants, using a unique study number, which was distinct from their study ID. Participants used lancets to prick their finger(s) in order to collect capillary blood and post it back to the provider as indicated by the kit instructions. The provider first communicated the results to me, and then I communicated these to both the participant and the participant's GP with a letter. The letter informed the participant's GP on the type of test done, the date done, medication changes at baseline and progress at 6 months including weight loss, and the results, as a handover.

3.3.6.2.5 Adverse events

Adverse events (AEs) related to physical health in people following the TDR programme have been extensively assessed and reported in previous studies. One previous trial reported no serious adverse events (SAEs) due to the TDR, whereas another reported two SAEs potentially related to the TDR intervention in the same participant [27,103]. Evidence shows that one in five people in the TDR intervention experience an adverse, mostly mild, event[27]. The most common AEs reported were constipation, headache, fatigue, and dizziness; they however occurred in a minority of participants (<8% each) and disappeared over time, when reported in previous studies [27,103]. As

the AEs of TDRs are well established, I decided, after discussing with my supervisors, to collect all AEs, but only report serious or severe (but not mild or moderate) AEs for this study.

Participants in both groups were asked to report potential AEs on REDCap at each follow-up. AEs in the intervention arm were also reviewed on each intervention delivery phone call. Participants in the control group also had the contact details of the team to contact them regarding any potential AEs. AEs were assessed using open-ended questions/textbox. Once reported by participants, they were then reviewed by the study GP to determine which ones were serious or severe.

3.3.7 Retention and withdrawal

Intervention participants received all the TDR products and the dietetic support for free. The control arm was offered reimbursement in the form of vouchers worth £10 at each follow-up (excluding screening/baseline). Finally, if participants agreed to an additional qualitative interview, they were also offered a voucher worth £15.

The intervention delivered was intensive, with calls occurring every other week, demanding a significant time commitment for participants. It was hypothesised that remote delivery over the phone, at the participants' preferred time, would be beneficial to adherence. There is some evidence that remote delivery facilitates better retention for some [193], as participants do not have to work around travelling to appointments or miss work.

The first intervention phone call with participants was arranged via email. Subsequent phone calls were usually arranged in the end of the previous phone call. If participants did not answer the phone for a scheduled appointment, an e-mail was sent for them to contact the study team to book another appointment. The threshold was set to 3 scheduled phone call attempts or not attending phone-call appointments for 4 consecutive weeks (excluding planned holidays, sickness etc.) before stopping further engagement and considering them intervention drop-outs.

At the start and during the course of the study, participants were informed in the PIS that they had the right to withdraw early from the intervention at any time. This could happen for several reasons, including but not limited to:

•The occurrence of what the participant perceives as an intolerable AE

•Inability to adhere to the intervention

•Participant decision

In addition, the study team could discontinue a participant from the intervention at any time if we considered it necessary for any reason including, but not limited to:

•Pregnancy

•Ineligibility (either arising during the study or retrospectively having been overlooked at screening)

•Significant protocol deviation

•Significant non-adherence with treatment regimen or study requirements

•Clinical decision

•Severe adverse event

When I identified concerns in participants in the intervention arms, through significant increases in their EDE-Q scores above clinical cut-off or clinical encounter or concerning response on PHQ-9, I discussed with my supervisors with view to inform their GP of our concerns. Communication to the participant's GP was planned to be done in writing via nhs.net e-mail, in order to ask them to consider assessing the patient and consider whether to refer to specialist services and/or other support in primary care.

Participants could stop the intervention but were encouraged to remain on study follow-up, as they continued to receive the standard follow-up assessment invites for the study. However,

participants could also withdraw their consent, meaning that they could withdraw from the study completely. Participants could withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal. They could also withdraw their consent and decline for their data and samples obtained up until the point of withdrawal to be retained for use in the study analysis, so in this case these would be erased and destroyed respectively.

3.3.8 Statistical analysis

3.3.8.1 Descriptive statistics

I used descriptive statistics to characterise the recruited sample in terms of baseline age, ethnicity, gender, socioeconomic status (by proxy, using index of multiple deprivation [IMD][194]), clinical characteristics (years of living with T2D, number of T2D medication, number of blood pressure medication and number of medication prescribed for anxiety/depression, baseline HbA_{1c}), as well as baseline disordered eating, its clinical impairment and quality of life. I used mean and SD for continuous variables. I reported categorical variables using count and percentages.

I also used descriptive statistics to characterise the population of eligible people who filled in the survey, regardless of randomisation, in order to define the mean score of disordered eating and clinical impairment, and their SD. The latter was used as the study's non-inferiority limits.

The CONSORT 2010 guidelines were followed to report participant flow; I also used descriptive statistics to report on recruitment, drop-out, and adherence to intervention.

3.3.8.2 Definition of population for analysis

The intention-to-treat population was used for the primary analysis, defined as all those randomised, regardless of the treatment that they received. To assess the robustness of the non-inferiority conclusion, I also conducted a secondary analysis in the per-protocol population (according to adherence)[195], including intervention participants who achieved at least 5% weight loss at 6 months, and excluding participants in the control arm who followed a TDR programme at any time during the first 6 months.

3.3.8.3 Statistical analysis of primary, secondary and exploratory outcomes

The non-inferiority limit was set to +1 SD for both the primary outcome (EDE-Q) and the two secondary outcomes (all EDE-Q subscales and CIA). Each continuous endpoint was assessed with a linear mixed-effects model with repeated measures adjusting for treatment group, timepoint, and baseline minimisation factors as fixed factors and participant as a random effect. The treatment effect was given by including a timepoint X treatment group interaction term. Missing data were handled through the mixed-effects model. Each model used all available endpoint data and assumes data were missing at random. Non-inferiority was assessed comparing the upper limit of the two-sided 90% CI of the adjusted difference in the global EDE-Q score at the end of the programme at 6 months with the non-inferiority limit of +1 SD. Likewise, the same principle was applied for all sub-scales of the EDE-Q as well as the CIA. The null hypothesis was set that the experimental treatment is inferior to the standard treatment, and the alternative hypothesis was hypothesised to be that the experimental treatment is non-inferior to the standard treatment. Sensitivity analysis with a two-sided 95% confidence interval to assess superiority was also conducted for the primary and secondary outcomes.

Linear mixed-effects models with the same approach as with the primary and secondary outcomes were used to determine the between-group differences for the effect of the intervention on exploratory continuous outcomes.

The regression models tested the null hypothesis that there was no intervention effect on each outcome. The null hypothesis was tested against a two-tailed P value of alpha=0.05. Scores at each time point were summarised by the treatment group using means and SDs.

Between-group differences for all outcomes were reported as adjusted differences, associated 95% and 90% CIs, and their p values.

Differences in the number of prescribed medications for diabetes and hypertension between groups at 6 months were compared using the Mann–Whitney U test, as variables were not normally-distributed.

All statistical analyses were conducted using R Studio, an integrated development environment for the R software, version 4.3.2 [121]

3.3.8.4 Data monitoring and ethics committee

Due to the main focus and the higher risk for eating disorders of the population under study, a DMEC committee was formed, consisting of a chair who is an academic clinician in eating disorders, an expert in obesity, and a statistician with significant experience in the field, all independent of the sponsor with no competing interests. The committee's role was to safeguard the interests of trial participants, assess the safety of the interventions during the trial, ensure continued trial integrity, scientific value, and ethical treatment of study subjects and monitor the overall conduct of the clinical trial. I prepared the progress reports using descriptive data for the committee and held meetings with them 5 months after the start of the recruitment and every 3 months thereafter.

In assessing day-to-day safety, an "amended" version was compiled to use throughout the intervention (see Appendix for the amended version of the EDE-Q). This was amended to remove items that would necessarily change if participants adhered to the TDR programme- for example, participants were asked about excluding particular foods, which participants on a TDR must do. Leaving these in would have led to spurious increases in one arm and mask true changes in psychopathology, if they arise.

3.4 Results

3.4.1 Recruitment and participant characteristics

The advert went live on the 8/03/2023 on both social media and Google adverts; I stopped Google adverts after 4 weeks, as traffic was much lower and I thought it did not justify the cost (contributing only just about 15% of completion of surveys at that point). The overall cost was £3,300 and it helped me recruit 56 participants on time and within budget.

The flow of the study, including recruitment, can be found in detail on Figure 3.3.

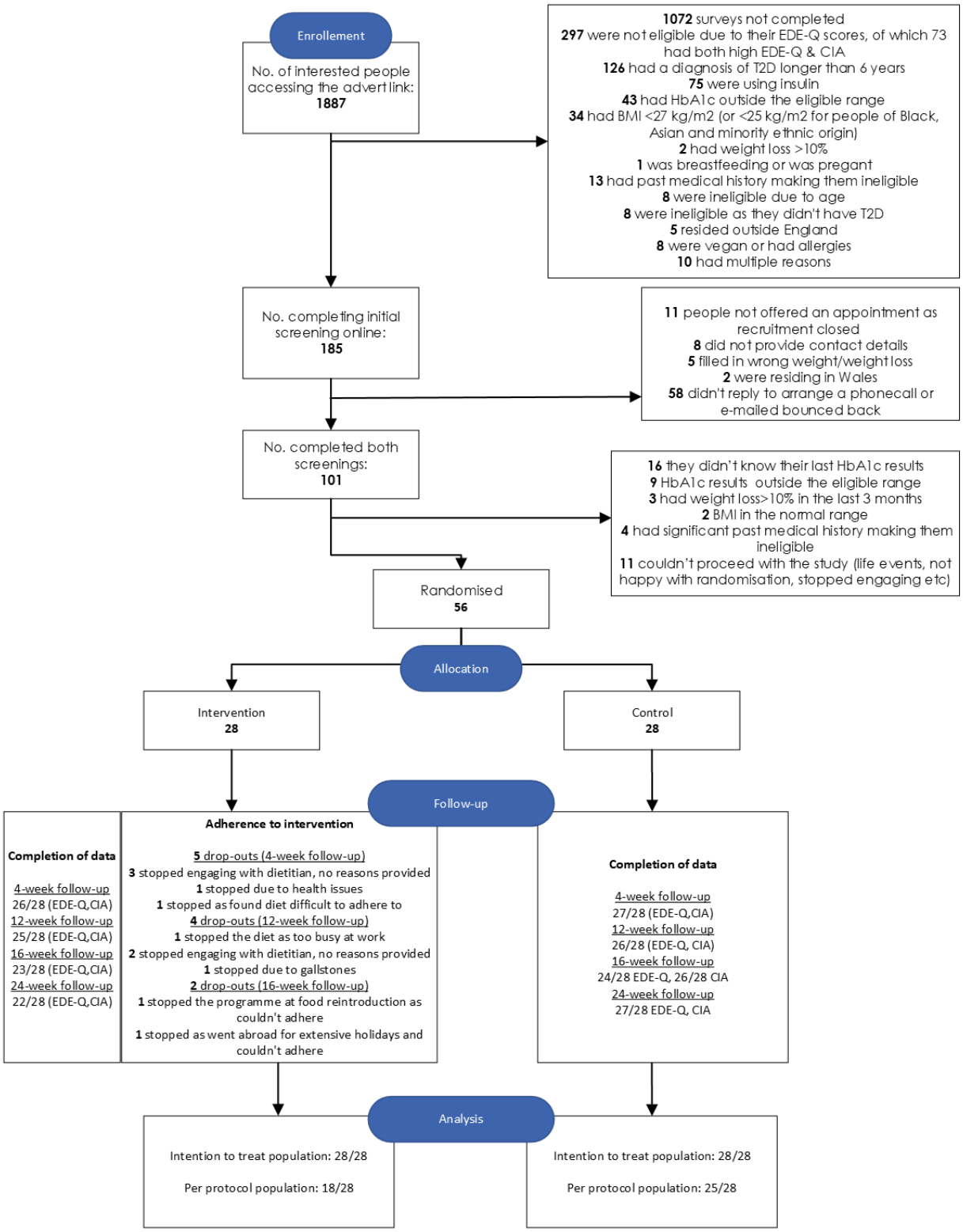
There were 307 responses from people living with T2D, diagnosed in the last 6 years, living with overweight/obesity, aged 18-65 years, living in England, who had an EDE-Q ≥ 2.67; their mean EDE-Q Global score was 3.75, with an SD of 0.72, which was used as the non-inferiority limit. For CIA, the sample was 288 people, with a mean score of 23.4 and a standard deviation of 11.1. EDE-Q sub-scale means and SDs are also presented in Table 3.5 below.

Table 3.5 Means (SDs) of the population deemed meeting the eligibility criteria. These SDs were used as non-inferiority limits

EDE-Q Global, Mean (SD) *(n=307)* Restraint Weight Concern Eating Concern Shape Concern	3.75 (**0.72**) 3.04 (**1.53**) 4.16 (**0.79**) 2.96 (**1.5**) 4.84 (**0.74**)
CIA, Mean (SD) *(n=288)*	23.4 (**11.1**)

Of the 101 people who I had phone calls with to confirm eligibility, 45 were ineligible, mostly due to not knowing their latest HbA_{1c} (n=16), HbA_{1c} not eligible once obtained from records (n=9) or having life events stopping them from proceeding with the study/declined randomisation (n=11). All reasons are displayed on Figure 3.3 below. The first participant was randomised on the 15/03/2023 and the last was randomised on the 20/09/2023, as the advert (or "campaign") was open on and off for a total of 18 active weeks depending on my capacity to respond to the demand, while delivering the intervention and running the trial. From the end of June 2023, I had administrative help from a trials administrator, primarily with scheduling follow-up surveys to be sent to participants, monitoring replies, and sending through thank-you vouchers, which freed up some of my time to re-start working on other DPhil projects.

Figure 3.3 Trial flow diagram



Randomised participants had a mean age of 49.9 years, 62.5% were women and were predominantly of White ethnic background. They had an average BMI of 39.6 kg/m^2 and no gross imbalances were observed, bearing in mind the sample size, in deprivation, based on the index of multiple deprivation (IMD)[194]. Participant's baseline characteristics are displayed in Table 3.6.

On visual examination of differences between groups, baseline characteristics were not significantly different between intervention and control groups, given the relatively small numbers per arm.

Four participants in the intervention group had a diagnosis of fibromyalgia and therefore were on medication for this that is also indicated for use in anxiety/depression. This medication was not counted in the total number of medications for depression or anxiety.

Table 3.6. Baseline Characteristics

	Intervention (n=28)	**Control** (n=28)	**All** (n=56)
Age[†], years	50.7 (8.0)	49.2 (8.2)	49.9 (8.1)
Gender			
Female	67.9% (19/28)	57.1% (16/28)	62.5% (35/56)
Male	32.1% (9/28)	39.3% (11/28)	35.7% (20/56)
Non-binary/other		4.6% (1/28)	1.8% (1/56)
Ethnic group			
White	100% (28/28)	92.9% (26/28)	96.4% (54/56)
Black			
Asian		7.1% (2/28)	3.6% (2/56)
Mixed or other			
Index of multiple deprivation			
1-3 (most deprivation)	14.3% (4/28)	21.4% (6/28)	17.9% (10/56)
4-7	60.7% (17/28)	57.2% (16/28)	58.9% (33/56)
8-10 (least deprivation)	25% (7/28)	21.4% (6/28)	23.2% (13/56)
Body mass index[†], kg/m^2	39.9 (8.5)	39.4 (7.2)	39.6 (7.8)
Weight[†], kg	110.4 (21.6)	116.4 (25.4)	113.4 (23.6)
Height[†], m	1.67 (0.12)	1.71 (0.11)	1.69 (0.12)
HbA$_{1c}$[†], mmol/mol	59.9 (11.9)	58.5 (11.9)	59.2 (11.8)
Duration of diabetes[†], years	1.4 (1.5)	2.2 (1.8)	1.8 (1.7)
Relevant Medication[†]			
Number of diabetes medications	1.0 (0.7)	1.3 (0.9)	1.2 (0.8)
Number of antihypertensive medication	0.8 (0.8)	0.8 (1.0)	0.8 (0.9)
Number of medications prescribed for mental health problems (depression, anxiety)	0.4 (0.6)	0.5 (0.6)	0.4 (0.6)
EDE-Q Global	3.3 (0.3)	3.4 (0.4)	3.3 (0.4)
Restraint	2.5 (1.1)	2.8 (1.4)	2.6 (1.3)
Weight Concern	3.9 (0.7)	3.7 (0.6)	3.8 (0.7)
Eating Concern	2.1 (1.2)	2.7 (1.0)	2.4 (1.1)
Shape Concern	4.6 (0.6)	4.4 (0.7)	4.5 (0.6)
CIA	22.1 (12.5)	18.7 (9.1)	20.4 (11.0)
PAID	47.2 (22.3)	47.5 (18.0)	47.4 (20.1)
PHQ-9	10.9 (6.8)	10.7 (5.2)	10.8 (6.0)
Continuous variables[†] *presented as mean (SD), categorical variables presented as %*			

3.4.2 Adherence and data completeness

3.4.2.1 Adherence to allocation group

Sufficient adherence to the study allocation was specified as weight loss of at least 5% at 6 months compared to baseline for the intervention and self-report of not using total diet replacement at 6 months for the control group respectively. Around 77% (43/56) were deemed adherent to their allocated group at 6 months; 18/28 (64.3%) in the intervention arm and 25/28 (89.3%) in the control arm.

Participants in the usual care group could have access to weight loss, as part of standard care available to them, depending on their catchment area. The majority though reported they followed their own diet (67.9%), with the rest either accessing weight loss on the NHS via referral or less so, privately.

3.4.2.2 Adherence to the intervention

The average number of sessions attended in the intervention arm was 9 (SD 4.6); the standard maximum number of sessions (without additional sessions for support) was 14 in the course of 24 weeks.

Of the 11 people in total who dropped out of the intervention, five stopped the intervention in the first month; three participants stopped engaging with me as the intervention dietitian with no reason provided, one stopped due to health issues (fibromyalgia flare-up and did not want to continue), and one stopped as they found the diet difficult to adhere to. By three months, another four people stopped the intervention; two participants stopped engaging with me as the intervention dietitian with no reasons provided, one stopped due to intense work commitments and one stopped due to issues with gallstones and they were advised to stop the diet by their GP. Two people stopped the intervention at four months; one went abroad for extensive holidays and could no longer adhere to the programme and one stopped engaging.

3.4.2.3 Data Completeness

Baseline data completion was 100% for all variables.

Completion of data for the EDE-Q was 94.6% at 4 weeks, 91.1% at 12 weeks, 83.9% at 16 weeks and 87.5% for the primary outcome at 24 weeks. For the CIA, completion of data was 94.6% at 4 weeks, 91.1% at 12 weeks, 87.5% at 16 weeks and 87.5% at 24 weeks. For the PHQ-9 and the PAID, completion of data was 91.1% at 12 weeks and 87.5% at 24 weeks. Competition of weight data was 91.1% at 12 weeks and 87.5% at 24 weeks (participants in the control group were asked only to complete their weight at 12 and 24-week follow-ups). Data completeness for the number of medications at 24 weeks was 87.5%.

The following table shows the % completion of data per arm.

Table 3.7 Data completion percentage per arm on each follow-up

	EDE-Q	CIA	PHQ-9	PAID	Weight
4 weeks					
Intervention	92.9%	92.9%	N/A	N/A	N/A
Control	96.4%	96.4%	N/A	N/A	N/A
12 weeks					
Intervention	89.3%	89.3%	89.3%	89.3%	89.3%
Control	92.9%	92.9%	92.9%	92.9%	92.9%
16 weeks					
Intervention	82.1%	82.1%	N/A	N/A	N/A
Control	85.7%	85.7%	N/A	N/A	N/A
24 weeks					
Intervention	78.6%	78.6%	78.6%	78.6%	78.6%
Control	96.4%	96.4%	96.4%	96.4%	96.4%

At 24 weeks, 1 (3.6%) participant in the control arm and 6 (21.4%) participants in the intervention arm did not complete the follow-up. Of these 6 participants, 5 had dropped out of the intervention; the 6th was a protocol deviation, as they were offered the NHS Path to Remission programme after being randomised to the intervention arm, and they preferred it over the study programme.

Participants who stopped the intervention/engaging with the study dietitian were more likely to stop filling in the follow-up surveys compared with intervention participants who remained

engaged with the intervention. A drop-out of 25% was accounted for in the sample calculation in the whole sample, therefore there was enough power in the remaining sample at 24 weeks.

3.4.3 Intention-to-treat population

Trajectory of EDE-Q, EDE-Q subscales, CIA, PHQ-9, and PAID throughout the first 6 months are shown in detail in Table 3.8 below.

3.4.3.1 Primary outcome: EDE-Q

For the intention-to-treat population, the linear mixed-effects model showed that the between-group difference in the EDE-Q score was - 0.8 points (90% CI -1.3 to -0.4) at 6 months (24 weeks); the upper end of the two-sided 90% CI was below the $d_{EDE\text{-}Q}$= +0.7 points, therefore non-inferiority was shown. In addition, given the 95% CI was between -1.4 to -0.3, the intervention was superior compared to usual care in terms of disordered eating.

Figure 3.4 Global EDE-Q mean scores and SEs, from baseline to 6 months for intervention (blue) and control (orange) arms

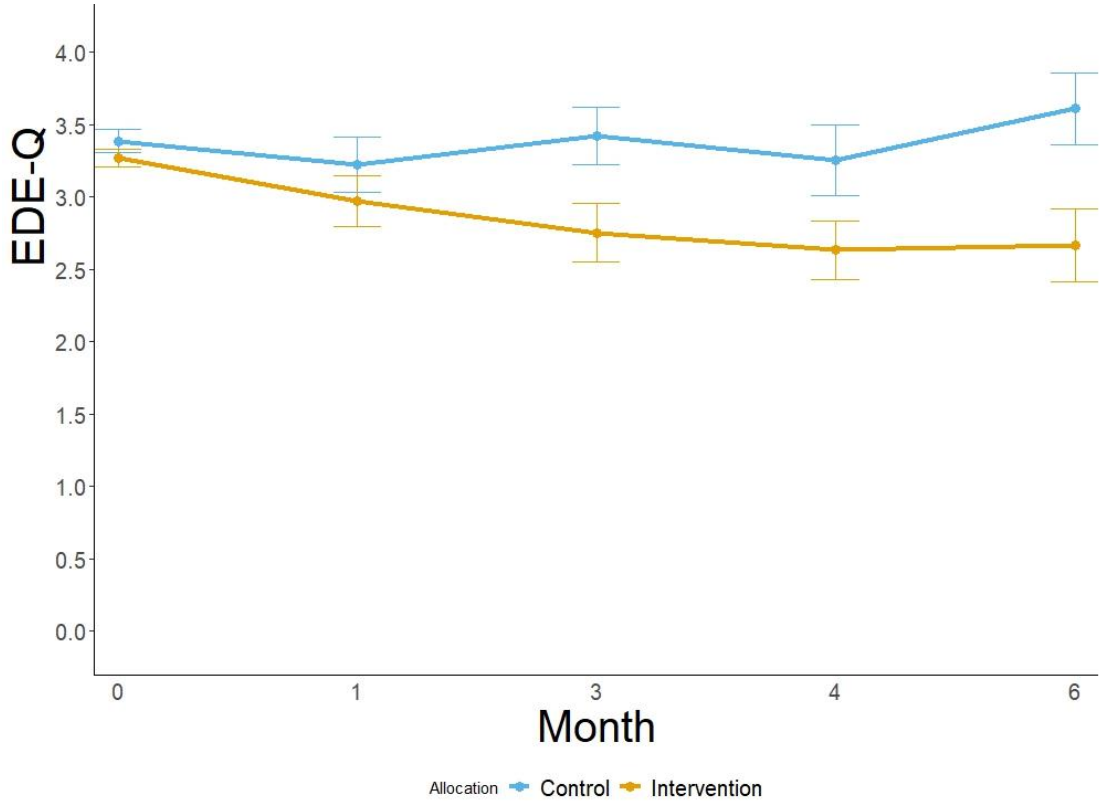


Table 3.8 Primary, secondary, and exploratory outcomes by group allocation, for the intention-to-treat population

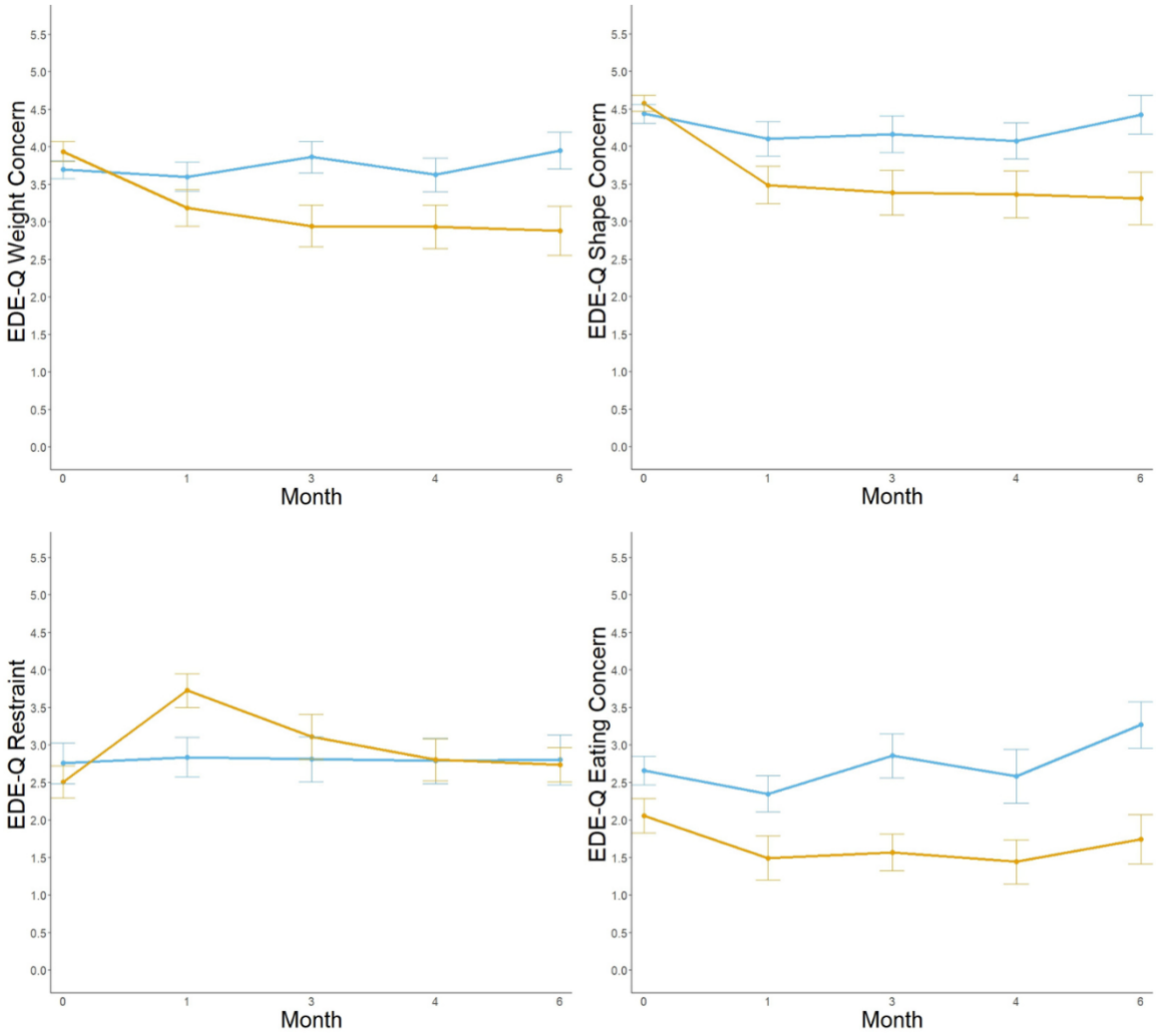
Outcome	Mean (SD) change from baseline				Adjusted difference (95% CI)	90% CI	P value
	Usual care group	No	TDR group	No			
3 months							
Weight change (kg)	-4.0 (5.5)	26	-11.8 (8.2)	25	-8.0 (-11.7, -4.3)		p< 0.001
EDE-Q Global score	0.0 (1.0)	26	-0.6 (1.0)	25	-0.5 (-1.1, -0.01)	(-1.0, -0.1)	p=0.01
EDE-Q Restraint	0.03 (1.9)	26	0.7 (2.0)	25	0.6 (-0.2, 1.4)	(-0.1, 1.3)	p=1.4
EDE-Q Weight Concern	0.2 (1.1)	26	-1.03 (1.1)	25	-1.2 (-1.8, -0.6)	-(1.7, -0.7)	p< 0.001
EDE-Q Eating Concern	0.1 (1.6)	26	-0.5 (1.4)	25	-0.7 (-1.4, 0.1)	(-1.3, -0.01)	p=0.1044
EDE-Q Shape Concern	-0.3 (1.2)	26	-1.3 (1.3)	25	-1.0 (-1.6, -0.3)	(-1.5, -0.4)	p=0.001
CIA	4.5 (13.8)	26	-6.7 (10.9)	25	-10.77 (-16.4, -5.2)	(-15.48, -6.1)	p< 0.001
PHQ-9	0.9 (5.1)	26	-3.4 (6.3)	25	-4.19 (-7.2, -1.2)		p= 0.001
PAID	1.9 (24.1)	26	-16.6 (19.8)	25	-17.94 (-28.1, -7.6)		p< 0.001
6 months							
Weight change (kg)	-3.7 (7.9)	27	-13.9 (11.2)	22	-10.2 (-14.2, -6.2)		p< 0.0001
EDE-Q Global score‡	0.2 (1.4)	27	-0.6 (1.2)	22	- 0.8 (-1.4, -0.3)	(-1.3, -0.4)	P=0.0035
EDE-Q Restraint*	0.1 (2.2)	27	0.4 (1.6)	22	0.2 (-0.6, 1.1)	(-0.5, 1.0)	p=0.56
EDE-Q Weight Concern*	0.2 (1.5)	27	-1.2 (1.3)	22	-1.4 (-2.0, -0.8)	(-1.9, -0.9)	p=0.012
EDE-Q Eating Concern*	0.6 (1.9)	27	-0.3 (1.6)	22	-0.9 (-1.7, -0.1)	(-1.6, -0.3)	p=0.031
EDE-Q Shape Concern*	0.0 (1.5)	27	-1.3 (1.5)	22	-1.4 (-2.0, -0.7)	(-2.0, -0.8)	p< 0.0001
CIA*	5.8 (14.9)	27	-9.1 (11.4)	22	-14.4 (-20.0, -8.7)	(-19.3, -9.7)	p< 0.0001
PHQ-9†	2.1 (7.2)	27	-3.6 (4.8)	22	-5.9 (-8.8, -3.0)		p< 0.0001
PAID†	0.8 (22.0)	27	-18.4 (18.0)	22	-19.2 (-29.4, -9.0)		p< 0.0001
Diabetes medication no†	0.1 (0.3)	27	-0.7 (0.8)	22	Mann–Whitney U test, w=484.5		p< 0.0001
Hypertension medication no†	0.0 (0.0)	27	-0.5 (0.6)	22	Mann–Whitney U test, w=445.5		P= 0.0001

‡ Primary outcome
* Secondary outcome
† Exploratory outcome
For all questionnaires, a higher score indicates worsening of symptoms/psychopathology/impairment/distress.
A reduction in the score from baseline indicates improvement of symptoms/psychopathology/impairment/distress.

3.4.3.2 Secondary outcome: EDE-Q subscales

As shown on Table 3.8, there was no evidence that the EDE-Q Restraint subscale was non-inferior as the 95% CI crossed the lower limit of the non-inferiority bounds. However, for weight, eating, and shape concern non-inferiority was shown.

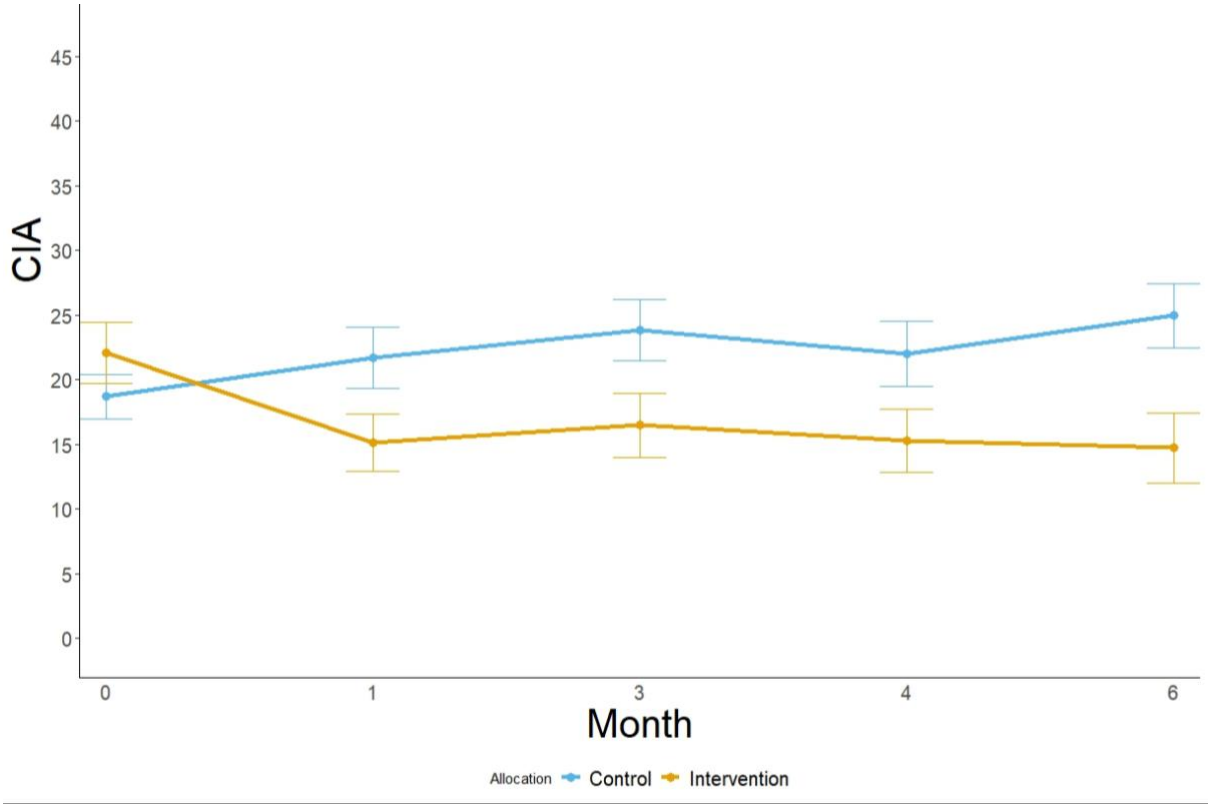
Figure 3.5 Sub-scale EDE-Q mean scores and SEs, from baseline to 6 months for intervention (orange) and control (blue) arms



3.4.3.3 Secondary outcome: CIA

The between-group difference in the CIA score was -14.4 (90% CI -15.48 to -6.06), therefore non-inferiority was shown (d_{CIA}=+11.1). In addition, superiority was also achieved, with 95% CIA -20.0 to -8.7. Observing within group changes, mean CIA score reduced in the intervention arm and increased in the control arm by the end of the 6 months.

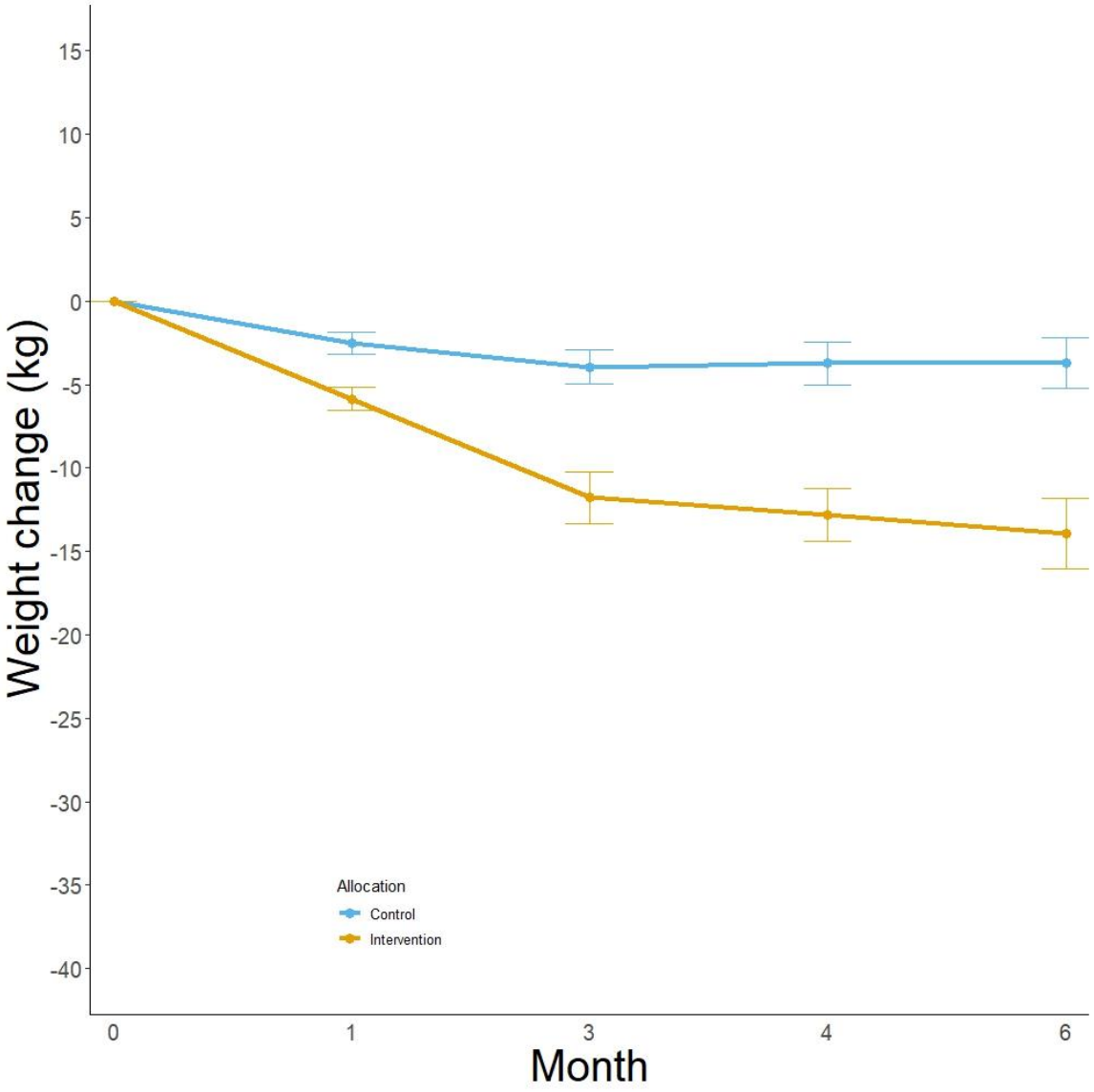
Figure 3.6 CIA mean scores and SEs, from baseline to 6 months for intervention (orange) and control (blue) arms



3.4.3.4 Secondary outcome: Weight change

Both groups lost weight; mean weight loss was -13.9 kg (SD 11.2) in the intervention arm and -3.7 kg (SD 7.9) in the control arm. The between group difference in weight was -10.2 kg (95% CI -14.2 to -6.2) at 6 months (intervention completion). In the intervention arm, 9 participants (32%) lost at least 15 kg at 6 months, whereas 13 participants (46%) lost at least 10 kg.

Figure 3.7 Weight change means and SEs, from baseline to 6 months for intervention (orange) and control (blue) arms



3.4.3.5 Exploratory outcome: Depressive symptomatology and diabetes distress

Quality of life was measured by proxy using scores describing symptoms of depression (PHQ-9) and diabetes distress (PAID), as described in section 3.3.4.2. The between-group difference at 6 months for PHQ-9 was -5.9 (95% CI -8.8 to -3.0), and for PAID was -19.2 (95% -29.4 to -9.0). The mean score for depressive symptoms in the intervention group reduced below the clinical cut-off of 10 and was above it in the control group. The mean diabetes distress scores reduced below the cut-off of 40 at 6 months in the intervention arm but not in the control. Mean scores at baseline for both groups were over these cut-offs, signifying moderate depression and severe diabetes distress respectively.

Figure 3.8 PHQ-9 means and SEs, from baseline to 6 months for intervention (blue) and control (orange) arms

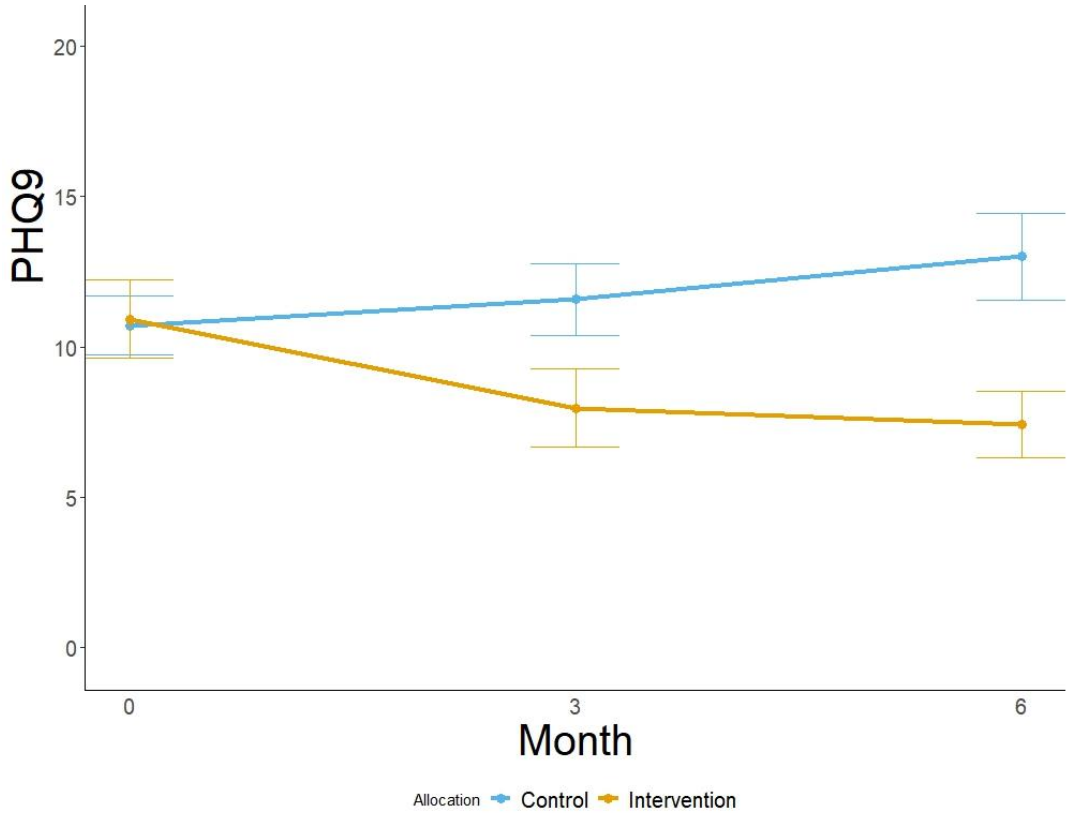
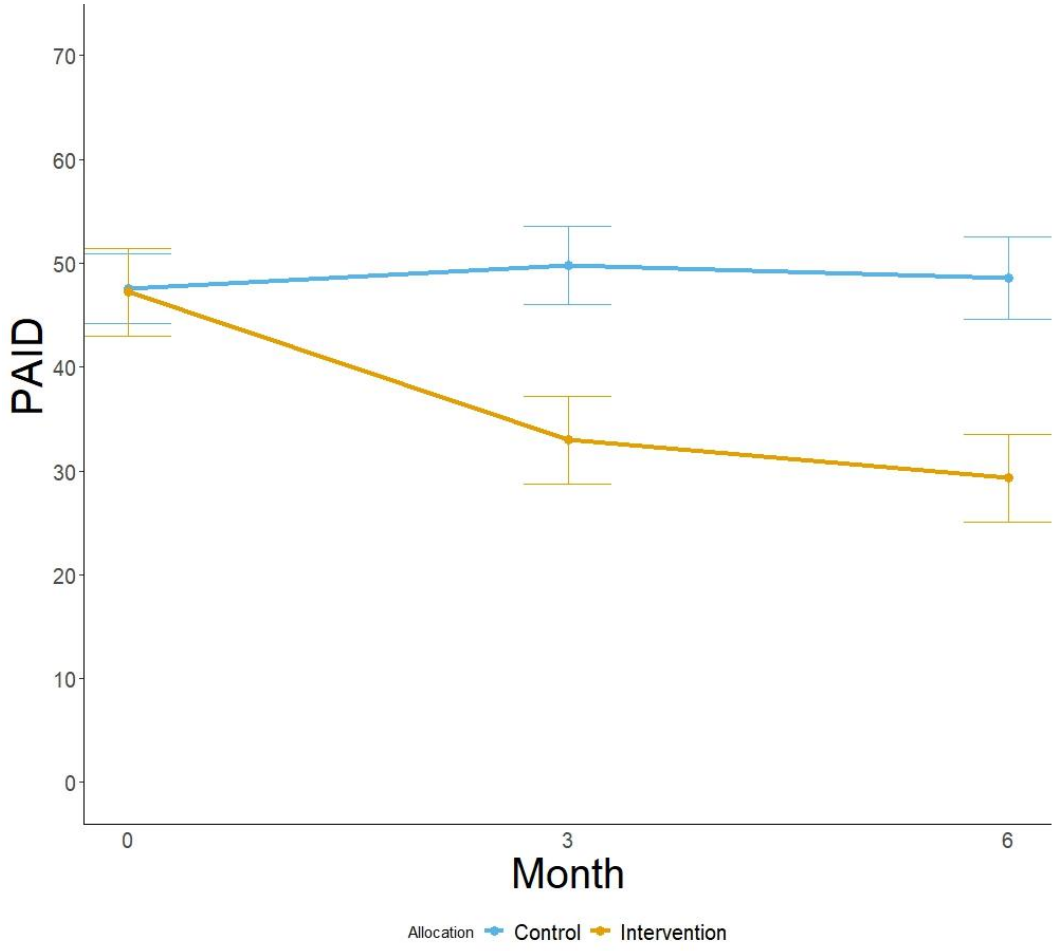


Figure 3.9 PAID means and SEs, from baseline to 6 months for intervention (blue) and control (orange) arms



3.4.3.6 Exploratory outcome: Changes in medication

Following the NHS guidance on titrating medication when starting the programme[167], intervention participants stopped at least one glucose and one blood pressure medication on the same day they started consuming TDR products in place of regular food. Participants were asked to self-monitor blood glucose and blood pressure, following the same NHS guidance; not everybody managed to maintain acceptable levels by the end of the programme, as these often depend on weight loss and by proxy, adherence to the programme. As a result, people who didn't lose weight mostly returned to their baseline medication regimen.

During the course of the study, in the control arm, 24 participants had no changes in their diabetes medication number, whereas 3 participants had the addition of a new diabetes medication in their prescription. In the same arm, no participant experienced a change in hypertension medication.

In the intervention arm, 15 participants were on at least one less diabetes medication and 12 participants were on one less hypertension medication at 6 months compared to their prescription at baseline. Only one participant in the intervention arm was taking one more hypertension medication at 6 months compared to baseline.

Overall, both mean number of medications for diabetes and hypertension decreased in the intervention arm compared to the control arm, a statistically significant difference, as shown in Table 3.7.

3.4.3.7 Diabetes status at the end of the intervention

All participants provided their most recent (within 12 months) HbA_{1c} levels at baseline. HbA_{1c} home test kits were provided to participants in the intervention arm, at the end of the intervention, both to assess the effectiveness of the programme and whether remission was achieved, and for safe handover to primary care. The home test kits, despite being essential in delivering this trial remotely, were unfortunately not very successful with participants. Although it was convenient to use home blood test kits, these required multiple finger pricks. Consequently, many participants did not provide sufficient blood or declined to send a sample at all. I sent the kit to only 17 out of the 28 intervention participants, and it was only completed successfully by 8 participants. Data on HbA_{1c} at 6 months are available from 9 participants; one participant had their HbA_{1c} done in their surgery, therefore their results were communicated to me verbally.

The mean baseline HbA_{1c} in the intervention arm (n=28) was 59.9 mmol/mol (SD= 11.9). The mean difference from baseline in HbA_{1c} at 6 months for the 9 participants was -16.8 (SD= 11.8). At the 6-month timepoint, 5 participants were in the range of what is considered remission (HbA_{1c}<48 mmol/mol and at least 3 months off diabetes medication)[196], whereas another 3 were approaching remission, with HbA_{1c} at 48/49 mmol/mol and no diabetes medication for the last 3 months.

3.4.3.8 Safety

No participant was judged to be at high suspicion for having developed a new eating disorder. Therefore, no participant was referred to their GP for this reason.

Between the start of recruitment in March 2023 and the collection of primary outcome data for all participants, I held 3 meetings with the DMEC team. The enhanced observation log was completed at each meeting and scores/outcomes were discussed with the DMEC team and included a total of 8 participants from the intervention arm.

Two participants mentioned behaviours which could be associated with disordered eating; one mentioned overeating, but no mention of losing control over it, whereas another mentioned overeating in response to hunger, along with losing control. The former followed the intervention for ~1.5 months and lost 4.8 kg whereas the latter followed the intervention for just under 2 months and lost 3.5 kg. They both decided to stop the intervention which didn't seem to work well for them, they did not engage sufficiently and did not complete questionnaires.

Two others could not continue the intervention; one was not able to adhere and for the other, "life got in the way"; the former lost ~2 kg and stopped the intervention in the first month, whereas the latter lost ~8 kg following the intervention well for 1.5 months before struggling to adhere further to the intervention and regaining the weight. They both completed the questionnaires at follow-ups and their scores increased. I intended to signpost them to further resources on nutrition and mental health if at 12 months their scores remained above 4, as advised by the DMEC and discussed with my supervisors. In August 2024, only one had completed the 12-month follow-up and their EDE-Q score had reduced lower than their baseline score, and below 4, therefore it was not deemed necessary to contact them with resources.

Two participants mentioned some concerns they would lose control of their eating, but their scores decreased, and so did their weight, by 13 and 20 kg respectively. The DMEC asked me to monitor them as a precaution.

One participant had a large increase in scores (baseline EDE-Q score 3.8, increased to 5.1 at 6 months). They strongly adhered to the programme as they lost 18 kg (15.3% of their body weight). In the qualitative interviews, they reported their mental health had significantly improved. In extensive discussions with the DMEC and the participant, trying to unpick their responses and rationale, the overall impression was that the participant did not quite understand some of the questions and went for quite high scores, despite reporting the opposite when asked. I concluded their reported feelings were trustworthy and that no further action was needed.

One participant demonstrated increases in the EDE-Q scores, which then went back to baseline figures. They chose to discontinue the intervention due to a fibromyalgia flare-up and I took no further action.

A detailed section on adverse events can be found in section 3.5.5 below.

3.4.4 Per protocol population

The linear mixed model showed that the between-group difference in the EDE-Q score in the per-protocol population was similar to the intention-to-treat population, at -0.9 (90% CI -1.4 to -0.4) at 6 months (24 weeks), therefore non-inferiority was also shown. The 95% CI was -1.5 to -0.3, showing evidence that the intervention was also superior compared to usual care.

As with the ITT population, there was evidence of non-inferiority for the EDE-Q subscales of weight, eating and shape concern whereas there was no evidence of non-inferiority in the restraint sub-scale.

In terms of impairment related to disordered eating, non-inferiority was also shown, with a between-group difference of -18.0 (90% CI -23.3 to -12.8).

Weight change between the two groups was, as expected, more profound compared to the intention-to-treat population; -14.2 kg (95% CI -17.9 to -10.4).

Superiority was equally shown in all these secondary outcomes, except for restraint. Detailed results are presented in Table 3.9 below.

Table 3.9 Primary, secondary, and exploratory outcomes by group allocation, for the per-protocol population

Outcome	Mean (SD) change from baseline				Adjusted between-group difference (95% CI)	90% CI	P value
	Usual care group	No	TDR group	No			
6 months							
Weight change (kg)	-3.2 (7.9)	25	-17.1 (9.7)	18	-14.1 (-18.2, -9.9)		p<0.001
EDE-Q Global score‡	0.2 (1.4)	25	-0.7 (1.2)	18	-0.9 (-1.5, -0.3)	-1.4, -0.4	p=0.00061
EDE-Q Restraint*	0.1 (2.3)	25	0.5 (1.5)	18	0.5 (-0.4, 1.5)	-0.3, 1.3	p=0.28
EDE-Q Weight Concern*	0.2 (1.5)	25	-1.4 (1.3)	18	-1.56 (-2.3, -0.9)	-2.1, -1.0	p<0.001
EDE-Q Eating Concern*	0.5 (1.9)	25	-0.4 (1.6)	18	-1.0 (-1.9, -0.2)	-1.8, -0.3	p=0.027
EDE-Q Shape Concern*	-0.1 (1.6)	25	-1.5 (1.6)	18	-1.5 (-2.2, -0.7)	-2.1, -0.9	p<0.001
CIA*	6.4 (15.0)	25	-11.3 (10.7)	18	-18.1 (-24.2, -11.8)	-23.3, -12.8	p<0.001

3.4.5 Adverse events

Throughout the course of the 24 weeks, one serious adverse event was reported overall, in a participant in the intervention arm who had their gall bladder removed; it was also deemed as severe by the study GP.

Two other adverse events were also reported, which were deemed severe by the study GP. One was a participant in the usual care group who received a cancer diagnosis and subsequently had been having chemotherapy, whereas the other was an intervention participant who presented to the Accident and Emergency Department with chest pain, which was later thought to potentially be a panic attack or stomach acid.

Overall, 10 additional non-serious adverse events were reported; 9 in the intervention arm and 1 in the control arm.

3.4.6 Post-hoc analysis of primary outcome with imputation of missing data

To ensure the non-inferiority conclusion for the primary outcome stands, especially given the proportion of missing data in the intervention arm compared to the control group (78.6% versus 96.4%) at 6 months, a post-hoc analysis was conducted. A worst-case scenario approach was

taken, where the total of 6 participants in the intervention arm who didn't complete the 6-month follow-up were hypothesized to have scored an EDE-Q score of their baseline score plus 1SD at 6 months.

The linear mixed-effects model showed that the between-group difference in the global EDE-Q score in this population was -0.55 (90% CI -1.0 to -0.1, p=0.0475) at 6 months (24 weeks), therefore non-inferiority was shown in this case as well. The 95% CI was -10.8 to -0.02, showing evidence that the intervention was superior compared to usual care.

3.5 Discussion

This is the first study attempting to answer whether an intervention similar to the NHS Path to Remission programme can affect disordered eating in a manner worse than usual care available to people living with T2D and overweight/obesity in the UK. This study found no evidence that such a programme, when delivered to people with T2D, overweight/obesity, and disordered eating, was worse than usual care in terms of exacerbating disordered eating in the short term. It was also superior, reducing disordered eating significantly compared to usual care. The same was observed for clinical impairment and all EDE-Q subscales (weight concern, eating concern, shape concern) except for restraint, which was not significantly different at 6 months. Participants in both groups lost weight; however, participants in the intervention group lost 10 kg more than usual care at the completion of the intervention (6 months). Depression scores and diabetes distress were significantly reduced in the intervention arm compared to usual care. The intervention arm also experienced a significant reduction in medication for diabetes and hypertension, following the NHS guidance on titrating medication at the start of the programme.

3.5.1 Strengths

This study aimed to address an important research question with significant policy implications. The study recruited its full intended sample of 56 participants, with a good proportion of male versus female participants, compared to weight loss trials which often tend to recruit mostly

women[197], as well as a good proportion of people living in more deprived areas of England, who again are often underrepresented in behavioural intervention studies[198]. Data completion and participant retention was satisfactory. These aspects strengthen the findings and suggest that the results might be generalised to people living with T2D and overweight/obesity, many of whom will have disordered eating and may enrol in the Path to Remission programme[199].

Another strength of this study is using the EDE-Q questionnaire. It has been developed and validated against what is traditionally considered the "gold" standard of assessing disordered eating psychopathology, the Eating Disorder Examination (EDE), and demonstrates good agreement with this semi-structured interview and clinical diagnoses[153]. Eating behaviours are complex and can be best described as a spectrum, with a healthy relationship with food at one end and diagnosable eating disorders at the other. Even those with generally healthy eating habits can often eat in response to emotions (i.e. emotional eating) or avoid meals to control their weight. It only becomes an issue when this is causing significant distress and psychosocial impairment, and when it occurs regularly[57]. Therefore, I chose a questionnaire that views disordered eating as a spectrum and measures it as a continuous variable, supplemented by a questionnaire that measures clinical impairment. This approach is supported by other literature[200]. Using cut-offs in a tool that has been designed for continuous use, inevitably leads to somewhat arbitrary decisions[201]. I tried to avoid using cut-offs as much as possible by mainly relying on the continuous use of the EDE-Q, especially when assessing the primary outcome.

A final strength of the study was the registration of the protocol on ClinicalTrials.gov, including an analysis plan to avoid bias introduced during the analysis after data was collected.

3.5.2 Limitations

The study had some limitations. Recruitment was conducted exclusively online, primarily through social media advertising. As a result, only people owning computers or smartphones and an internet connection could have accessed the advert, potentially excluding more deprived people or those less proficient with technology. Baseline characteristics revealed that the sample

recruited was similar to previous studies' populations on visual examination, except for ethnicity, which remains a limitation.

The primary outcome assessment was conducted using the EDE-Q questionnaire. The questionnaire has been developed based on the EDE, which is considered the gold standard[202] in the field. Inevitably, a self-reported questionnaire is not the same as having an interview with a specialist; despite the adequate validation[153], there have been some concerns in the literature that the EDE-Q may overestimate binge eating frequency compared to EDE, which could inflate EDE-Q scores relative to the EDE. On the other hand, the EDE requires far more resources, time and effort by both the researcher and the participant[153], so it wasn't an option for this study. In addition, the study looked at the change in score, which somewhat negates this concern. Other questionnaires like Binge Eating Scale[203] would not be appropriate, as they measure one aspect of disordered eating (here binge eating severity), but not disordered eating psychopathology as a whole.

In the randomisation, as described in the methods, a 20% random element balancing gender (man/non-binary/other or woman) and EDE-Q global score (≥3.9 and <3.9) was used. The 3.9 cut-off for EDE-Q was based on previously reported means in populations with obesity and subclinical disordered eating[173,174]. However, due to the exclusion of participants with EDE-Q ≥4 and CIA score ≥16 at screening, the majority of participants had EDE-Q<3.9 which made the balance of stratification factors between groups less than optimal. It was expected that more participants would have an EDE-Q>4 without a CIA>16, but this was found to not be the case. Thankfully, baseline characteristics between groups were not significantly affected and appeared similar on visual examination.

As in the majority of interventions aiming at changing dietary behaviours[204], blinding of the participants in each arm as to what intervention they receive was not possible here. This remains a major limitation of the study, as knowing the intervention they were allocated to, participants

might alter their behaviour and the way they complete their follow-up assessments[205]. To minimise bias in this trial, randomisation was conducted by an independent researcher and participants self-completed the questionnaires in the study follow-ups. As a result, they were less likely to feel pressure to report an experience different to the one they had, as disordered eating behaviours are often associated with shame and guilt[206].

The non-inferiority limit was set at 1SD due to limited evidence of what the mean EDE-Q score is in this population, based on discussions with clinicians working in the field. I recognise this is a generous non-inferiority limit, as an increase in the mean score for this population of 1SD, would result in a ~34% increase in people's risk of developing an eating disorder. The fact that disordered eating in the intervention arm reduced significantly compared to usual care was a positive finding that helped avoid challenges in interpreting the results that may have occurred if there was an increase in the score compared to usual care.

Despite diabetes remission being the goal of the TDR programme, this study did not succeed in collecting enough data to show the proportion of intervention participants who met the criteria for remission at the end of the programme. Despite the provision of an HbA_{1c} kit, only half completed it successfully. As discussed in Chapter 4 and previous qualitative studies of similar programmes[192], remission is important to participants; it is unclear how this lack of certainty on whether participants achieved remission affected participants' feelings. This risk is somewhat mitigated by regular blood glucose monitoring using equipment provided for safety, as participants obtain instant feedback on their blood glucose management throughout the programme; despite not knowing if they achieved remission in the end, there might be strong indications based on consistently good blood glucose readings.

Finally, a major limitation of this study is that the trajectory of scores of participants who dropped out of the intervention and the study follow-ups experienced is unknown. There is a possibility that the small number who dropped out stopped engaging with the study due to shame and guilt

of being unable to adhere to the intervention, and/or increased disordered eating. Equally, they might have also felt that the intervention wasn't working for them, or couldn't follow or did not want to follow at this point. Fortunately, some participants who stopped the intervention continued to complete the follow-ups, leading to 87.5% completeness of data at 6 months, more than I accounted for in my sample size calculation. Reassuringly, the post-hoc analysis imputing missing data for the 6 participants in the intervention assuming their EDE-Q worsened by 1SD did not alter the conclusion of the study.

The NHS Path to Remission programme is delivered by a variety of providers commissioned by integrated care boards (ICBs) and subsequently, different healthcare professionals or coaches. Some providers employ dietitians whereas some employ coaches who don't necessarily have a nutrition qualification or other training. There is a reasonable possibility that some of the effect on disordered eating has to do with who delivers the programme and how they present the content to participants. This cannot be investigated as part of the present study.

3.5.3 Comparison with previous similar studies

Previous studies using TDR have shown significant weight loss and improvements in quality of life similar to the present study. The adjusted mean difference in weight in the DROPLET trial was −9.6 kg (95% CI −11.6 to −7.7 kg) at 6 months[103], whereas in the DiRECT trial, the adjusted difference in weight was at -8.8 kg (95% CI -10.3 to -7.3 kg) at 12 months[27]. In both trials, greater improvements in quality of life were observed in the intervention arm. In a similar intervention paired with physical activity and targeted at people with T2D, the adjusted mean difference in weight was -6·1 kg (SE 1.2) at 12 months, a weight loss which was maintained from 6 months and a similar improvement in quality of life[207]. The recently published early findings from the NHS Type 2 Diabetes Path to Remission Programme[158] showed average weight loss of -9·4 kg (95% CI -9.8 to -8.9, n= 1740, population with no missing data, who started the programme, of which 960 completed it). The improvement in mental health in the intervention arm compared to control, measured by the PHQ-9 and the PAID questionnaires is indeed a somewhat expected finding.

Previous systematic reviews looking at the impact of weight loss trials on health-related quality of life and mental health also showed similar improvements, using various tools to assess the outcome[98,99,208].

The systematic review and meta-analysis in Chapter 2 showed that weight loss programmes are associated with and probably reduce eating disorder symptoms at the end of the programme, while also producing significant weight loss. Global EDE/EDE-Q scores, as well as eating, shape and weight concerns sub-scales significantly reduced at the end of interventions, while restraint increased; observations consistently present in the results of the ARIADNE study. The systematic review examined the impact of TDR on disordered eating, however only two studies were included that used TDR as an intervention. The first study[122] included adults with BMI >27 kg/m^2, T2D and low EDE-Q scores at baseline, randomised to either receive a TDR programme paired with or without cognitive behavioural therapy (CBT); in both groups, EDE-Q scores reduced with no significant difference between arms. In the second study[128], a TDR component was added to pharmacotherapy and intensive behavioural therapy (IBT), versus pharmacotherapy and IBT, and IBT alone. The population comprised people with obesity (BMI 30-55 kg/m^2) and disordered eating at baseline. Similarly, scores in EDE-Q global scores, and all but restraint subscales reduced significantly from baseline in all groups with no evidence of differences between groups. Restraint increased in all groups (with the higher increase from baseline observed in the group with pharmacotherapy and IBT). The results of these two studies which incorporated TDR are similar to the results of the ARIADNE study.

3.5.4 Next steps: scope for expansion of sample size

The non-inferiority limit in this trial was decided based on discussions with relevant healthcare professionals and consulting the literature. However, if a change in the mean EDE-Q scores of 1 SD occurs, this would realistically lead to a prevalence of potentially diagnosable eating disorders change from ~2% to 15% in the population of interest. It would be helpful to translate this in real numbers; based on a study that looked into the epidemiology of T2D remission in Scotland[209],

there were around ~100,000 people who met the criteria to be offered the TDR programme for diabetes remission (this number was derived indirectly from the study group's descriptive statistics). In the DiRECT trial, from the total amount of people who were screened for eligibility, around 20% ended up starting the programme. If we assume the same percentage would start on the TDR programme in Scotland, if this was available to them, then 20,000 people would start the TDR. In the worst-case scenario that this programme worsened their disordered eating above the non-inferiority margin, instead of 400 people accessing eating disorder services (~2%), 3000 people only in Scotland would need a referral instead, which would put enormous pressure on an already stretched service.[210]

In conclusion, a bigger trial, with a more strict non-inferiority limit could offer additional reassurance in decision-making related to policy. This was eventually decided to be at 0.5 SD. If the maximum change allowed for non-inferiority would be an increase of EDE-Q global score equivalent to 0.5 SD from the population mean, then 138 people (n=69 per group) are needed to be 90% sure that the upper limit of a 90% two-sided confidence interval will be below the non-inferiority limit of 0.5 SD. Accounting for a 10% dropout, 154 participants (n=77 per group) are needed.

In discussions with policy stakeholders, we have secured additional resources to expand recruitment beyond the scope of this thesis. The expansion of the trial has received ethical approval and will include recruiting participants through NHS services.

The expansion of the trial will also offer the opportunity to address some other limitations of this trial. Programme providers will be blinded to participant scores throughout the programme. In addition, the effect on disordered eating might vary depending on who delivers it (coach, healthcare professional or others) and how they present the content of it to participants. Depending on how recruitment is spread regionally and if numbers allow, we could conduct a subgroup of analysis depending on the type of professional delivering the study, given the programme is commissioned to be delivered by different providers across the country.

3.5.5 Conclusions and implications

Overall, the results of the study show that a programme similar to the NHS Path to Remission can help people with disordered eating to lose weight successfully and offer reassurance that the programme will not aggravate their disordered eating and may improve it, at least in the short term. In addition, a significant reduction in depressive symptoms and diabetes distress following the end of the programme was observed. The ARIADNE study offers valuable new knowledge in the field, which has direct policy implications; the results can offer reassurance about the hypothesised risk of eating disorders associated with the programme, while it becomes part of managing T2D and overweight/obesity in the UK.

It seems that weight loss trials, and TDR programmes similar to the one offered in the ARIADNE study, reduce concerns around weight, shape and eating, as measured in the EDE/EDE-Q. This could be facilitated through reduction of weight and improvement in body image, which has been previously reported in the literature[211]. As discussed in Chapter 2, these tools were not designed to be administered to people participating in weight loss programmes, during which participants are encouraged to practice dietary restraint by default. Dietary restraint has over the years been characterised as an initial element in the development of eating disorders[212]. Restraint has also been postulated to be the trigger in the development of eating disorders[87]. A review appraising the literature on the subject concluded that restraint cannot be categorised as healthy or unhealthy, without first determining the context; when exercised as part of a validated weight loss programme, restraint appears not to relate to increased levels of eating pathology[80].

Most studies on weight loss often only follow participants up in the short term; longer-term follow-up is needed to evaluate whether the effect observed in the ARIADNE trial is maintained. The systematic review in Chapter 2 examined the longer-term effect of weight loss on disordered eating, however, the median duration in the long-term follow-up was around 10 months. Weight regain is common post weight loss interventions; a large systematic review showed that weight regain following the programme end was 0.12-0.32 kg/year greater in intervention compared to

the control group[213]. This systematic review showed that weight loss interventions resulted in an increase in quality of life at the end of the programme in the intervention arm, which however returned to baseline following weight regain. It is unclear whether a similar effect could be observed in disordered eating or worse, disordered eating increases in the long-term. Weight regain following TDR for diabetes remission has been observed in the DiRECT trial and most people will eventually gain at least some of the weight back and might return to having diabetes[38]. This could eventually have an impact on disordered eating psychopathology.

The expansion of the ARIADNE trial, to include more participants and to reduce the non-inferiority limit at 0.5 SD, will offer further reassurance about the impact of the programme on disordered eating both in the short and the long term; apart from follow-ups at one and two years, NHS data linkage will also offer the possibility to evaluate whether eating disorders develop years after the intervention has ended.

Chapter 4. Changes in eating behaviour and disordered eating symptoms during the intervention: a process evaluation using content analysis

4.1 Summary

Following from the previous chapter, the ARIADNE study attempted to investigate concerns from healthcare professionals, patients and the public on the impact of TDR on disordered eating remain. This was done by conducting a non-inferiority randomised control trial on the impact of a programme similar to the NHS Path to Remission on disordered eating in people with overweight/obesity, T2D and disordered eating at baseline. The study also included a qualitative sub-study, presented in this chapter. The aim was to assess why disordered eating changed during the TDR programme, in people with overweight/obesity, T2D and disordered eating at baseline. Content analysis of dietetic sessions was used to identify similarities and differences in the experiences of people participating in a TDR programme according to their EDE-Q score trajectories.

Participants with worsening disordered eating scores or of variable pattern throughout the trial reported eating usually in response to emotions and boredom and experiencing significant hunger during the TDR phase. This often resulted in non-adherence and unsuccessful attempts to return to the programme. In addition, these participants reported that environmental factors made adherence even harder. Participants who experienced stable or reducing disordered eating scores throughout the trial also experienced hunger but were often able to manage it and continue on the programme. The majority of participants regardless of score trajectories praised the ease of the programme and welcomed not having to make choices around food during TDR, but were anxious about transitioning to eating food again, and were pleased with the support they received to do so.

The barriers and facilitators reported in this study among participants with disordered eating align with studies of TDR in the broader population with obesity/T2D. For a large proportion of participants, the programme seemed to work well and their scores reduced; this qualitative sub-

study identified potential differences in experiences of the programme between people who had decreases or stability in their scores versus participants with increases in their scores and participants with variable EDE-Q trajectory, as well as similarities.

4.2 Introduction

A 2018 systematic review[214] of qualitative studies examining the experiences of people using low/very low energy diet (LCD/VLC) programmes to manage overweight/obesity summarised the motivation to undertake the programme, factors affecting adherence, acceptability and experiences, as well as reflections on weight maintenance upon completion. Some themes that stood out included poor health as a motivation to undertake the programme, motivation to decrease medication and to increase quality of life, as well as the support of participating in a scientific study. Participants in all studies included in the review felt that the LCD/VLCD programmes were easier than expected and that their simplicity and fast weight loss helped maintain adherence. After the completion of the programme, participants reported positive changes in their physical and mental health but also their concern about going back to old habits and desire for long-term support. The DROPLET study team[215], more recently, also interviewed some of their participants, providing insights into their experience. Improvement in physical health was identified as a motivation to lose weight. In that study, most participants mentioned having previously attempted to lose weight, unsuccessfully, multiple times. A key motivator to participate was the expectation of successful and significant weight loss with TDR. Similarly to the systematic review, participants highlighted the improvement in physical and mental health. In the DiRECT qualitative study[192], experiences were similar, with the addition of diabetes remission as a motivator. In a recent study[216] of TDR use for weight loss before colorectal cancer surgery, participants also reported previous unsuccessful attempts to lose weight, and motivation to undertake the programme with a view of improving surgical outcomes. Participants' concerns evolved around the palatability of the diet and possible side effects. In another study looking at

the experience of postmenopausal women using a very low-energy diet[214] at the end of the programme, participants reported that it was the ease of the programme that enabled its success, as they didn't have to prepare and make decisions around food. What is more, they felt that the cessation of their normal diet worked well in reconnecting with their hunger and satiety signals. Overall, these studies have some overlapping themes expressed by their participants around TDR. Despite the recent number of qualitative studies on experiences, barriers and facilitators of undertaking a TDR programme, these studies have not included questions about changes in participants' body image and eating behaviours and cognitions while on the programme. Furthermore, these experiences may differ in people with disordered eating at baseline.

As detailed in Chapter 3, the ARIADNE study was designed to investigate whether a low-energy TDR programme, similar to the one offered in the NHS Type 2 Diabetes Path to Remission is inferior to standard care in terms of increasing disordered eating in susceptible people with overweight/obesity and T2D. This qualitative study aimed to explore why/how changes in eating behaviour and disordered eating symptoms occurred, by analysing the discourse during the intervention sessions and grouping participants depending on their disordered eating score trajectories. I anticipated that different eating score trajectories would be reflected in the reported experiences of the programme. In addition, the overall themes emerging from participants in the programme, the barriers to and facilitators of the success of the programme, as well as their reported changes in eating behaviour and disordered eating symptoms were explored.

4.3 Methods

4.3.1 Recruitment and sampling strategy

The qualitative sub-study was embedded as part of an explanatory sequential mixed methods analysis[217]; the qualitative analysis followed the quantitative analysis, with the aim of exploration that enables answering the research question more deeply[218].

Intervention sessions were delivered between March 2023 and February 2024. The intent was to audio-record all dietetic sessions delivered to all 28 intervention participants if they were happy and consented verbally to it. Participants were informed that the interviews would be anonymised and handled confidentially and in line with standard information governance operating procedures. Originally, the intent was to prioritise participants who experienced at least 1 SD change in their scores; this revealed nine participants with a decrease of at least 1 SD and three with an increase of at least 1 SD in the sample. Eventually, I decided to include all participants to ensure a rich and diverse sample. Participants were grouped into those who experienced improving or worsening of disordered eating scores, participants with variable or stable trajectory and finally a sub-group was formed of participants whose scores rose above the cut-off of 4 which is usually used in the literature to signify increased risk of disordered eating[153]. The purpose of the subgrouping categories was to identify differences in the patterns of experience between subgroups.

4.3.2 Data collection

All dietetic sessions were delivered via telephone, using a study-specific landline operated via the University's safe Microsoft Teams platform. This offered the opportunity to directly audio-record sessions and automatically transcribe them. Due to using Microsoft Teams to audio-record sessions, it was not always possible to record calls for various reasons; for example, if participants missed a call and called the study landline back in their own time. Setting up the system also required time, so, in back-to-back consultations, it wasn't possible to record sessions and maintain the schedule of calls without delaying calling the next participant. Few participants also appeared reluctant to have sessions recorded, so I used my discretion in whether or not to request a recording of every session to avoid potential dropouts. Striking a balance between the intent of the protocol and the practicalities of running the trial day-to-day, the target was revised to have at least one session per month recorded, when the vast majority of participants were set to receive 2 dietetic sessions per month. Therefore, sessions were recorded for 22 out of the 28

participants in the intervention arm. From the remaining six participants in the intervention arm that had no sessions recorded, one accepted the NHS Path to Remission programme offered via their GP, shortly after randomisation to the intervention and, therefore did not have their sessions delivered and recorded by me, the study dietitian. The remaining five participants dropped out of the intervention, either communicating this to the study dietitian or by not replying to phone calls before any sessions could be recorded. Three participants stopped before the two-week call which is the first recorded, one stopped at 6 weeks and one at 12 weeks (but without adhering to the programme until then). I also compiled a qualitative semi-structured interview guide. The intent was to use it for participants who did not continue with the intervention but agreed to have qualitative sessions.

Transcriptions were acquired automatically, using the artificial intelligence feature of the recording software; before coding, they were anonymised where necessary, checked for accuracy and corrected by listening to the recordings, resulting in 120 verbatim transcriptions. The number of sessions each of the 22 participants had recorded varied. The average number of transcripts per participant was 5.5 (SD 2.8) when the maximum standard number of sessions offered (without any additional sessions participants might need) was 14. In total, 55% of the participants (12/22) had more than 50% of sessions recorded and around 30% had more than 75% of their sessions recorded.

Transcripts were not returned to participants due to the large time gap between the sessions and the analysis.

In addition, I kept a reflexive diary while delivering the intervention, with the qualitative study in mind. I also kept memos in the dietetic notes while discussing with the 22 participants whose transcripts were included in the analysis, in case certain points of interest around changes in eating behaviour and disordered eating were not recorded on that particular occasion. This was done when necessary to add details essential to the transcription and to ensure in-depth data capture[219]. An example was the following: a patient felt guilty about the fact that went to a street

party on Saturday, ate food and drank alcohol- she actually almost felt sick of the food and also had a stomach bug ("I know it is stupid but the next day I continued with the programme.").

4.3.3 Positionality and self-reflection of potential biases

I had the opportunity to reflect on my positionality on three aspects of this work; the subject, the study participants, and the research context and process. This is an essential part of qualitative research[220], to comprehend my "pre-understanding" of these aspects and ensure the minimum possible bias of my influence was reflected in the planning of the study, analysis and interpretation of the data[221,222].

4.3.3.1 The subject

From the perspective of the healthcare professional, my understanding of the subject of obesity, T2D and disordered eating derives from my clinical practice as a dietitian previously working in the NHS, and my systematic review of the literature on obesity, weight loss and disordered eating. I have not previously worked in specialities offering dedicated services in eating disorders, obesity or T2D alone, but I have seen patients in my practice with these conditions, where they present with other symptoms (e.g. renal, gastroenterological). I have seen many patients with overweight/obesity and/or T2D but only a few cases with eating disorders, mainly with anorexia nervosa. As a result, I am not a specialist in the field and do not hold any strong anti-diet views that I have observed among many specialist eating disorders dietitians.

4.3.3.2 The participants

From the perspective of the patient, my lived experience involves having a close relative living for the last 20 years with obesity and T2D. I have observed first-hand the impact of the diagnosis, the evolution of the condition, and the role of diet and weight loss in managing T2D on the person and the family. I, therefore, expected I might relate to the burdens and anxiety people living with T2D and overweight/obesity face when it comes to managing the conditions through diet modification. I suspected this might affect the way I deliver the intervention, in treating participants with additional empathy and understanding during intervention delivery. However,

it is fairly consistent with how dietitians are trained to be compassionate and deliver patient-centred care, according to standards of professional conduct set by our governing body[223].

4.3.3.3 The context

From the perspective of the researcher and healthcare professional who delivers the intervention to participants and also conducts the analysis of the qualitative interviews, there is certainly a risk of bias but also a unique opportunity. The risk lies in that I am not blinded to the hypothesis of the study and the changes in disordered eating scores while delivering the intervention, asking questions and analysing the data; I considered this an important aspect to reflect on. However, I simultaneously hold a unique insight into the experiences shared with me as the dietitian delivering all the sessions to participants and keeping a reflection diary. I got the opportunity to become acquainted with the intervention participants and discuss regularly with them in the course of the 6 months of the intervention delivery. This might help balance some of the issues out, as it was often that participants repeated certain themes, which offered some reassurance in the reliability of what was captured.

4.3.4 Content of interviews

During the intervention sessions, participants typically discussed their experience, barriers, facilitators, and changes in eating behaviour and disordered eating symptoms.

Additionally, I attempted to maintain a balance between the delivery of a pre-specified intervention and the need to conduct qualitative research; my questions revolved around how participants coped with adhering to the programme, any issues they faced and physical/mental health check-ins while navigating the stages of the interventions. Exploration of specific aspects of participants' experiences was opportunistic when participants felt they wanted to share and elaborate on them.

4.3.5 Selection of the method of analysis

The analysis process followed qualitative content analysis with a predominantly inductive approach described by Elo and Kyngäs[221]. The main aim was to identify the reasons behind the changes or lack thereof, in disordered eating, therefore a degree of deductive analysis was

employed, to ensure the open-coding answers the research question[224]. As a result, the analysis and formation of codes was done with the cognitive behavioural theory[70] theory broadly in mind. According to this, disordered eating could result from failing to achieve weight loss by following rigid dietary rules. Efforts to adhere to extreme and highly specific rules can break down, for example at times of negative emotion, and temporary abandonment of the rules. This could lead to a vicious cycle of imposing even stricter rules and further breaking them, e.g. having 3 products the next day to account for eating food the day before. This stems from overvaluation of eating habits, shape or weight, as people with disordered eating largely judge themselves against these, in contrast to most people, who evaluate themselves on their performance in other domains of life (e.g. work, parenting, relationships). If other patterns arose from the data in connection to experiences, barriers and facilitators while in the intervention, these could also form different codes and categories.

Content analysis was deemed the most appropriate method of analysis[225], given the large volume of data and the means of data collection (i.e. recording dietetic sessions with participants) which did not involve directly asking people questions on a specific topic, here disordered eating related to the intervention.

4.3.6 Data analysis

Transcripts were divided into three stages according to the intervention timeline; TDR phase, food re-introduction phase, and end of programme. The reflexive diary and dietetic notes were also reviewed.

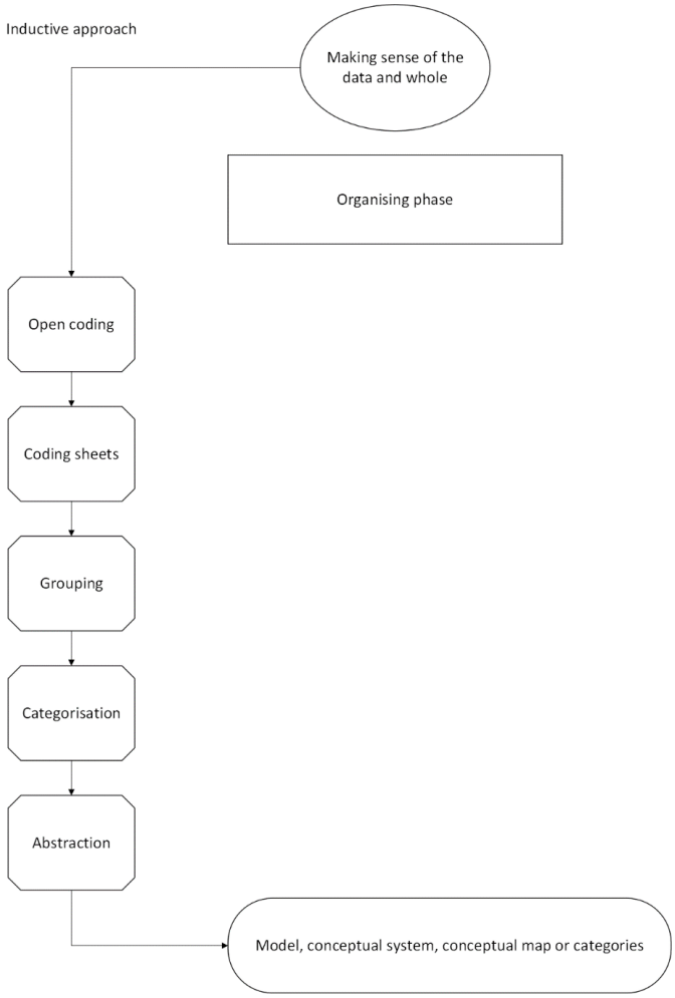
Transcripts and notes were read multiple times and data were coded openly to form headings to describe all aspects of content[226,227]. Headings were then gathered onto coding sheets, to generate codes. Once transcripts were coded, individual score trends of the 22 participants were reviewed and participants were divided into 4 categories depending on their quantitative EDE-Q score trajectories; reducing trend (improving) scores, approximately stable scores, increasing (worsening) scores, and variable trend (where scores went up and down significantly). There were

only two participants with stable scores, therefore were incorporated into the improving EDE-Q category, on the basis that participants in this category did not experience worsening scores. As a result, three categories were compared in the end. A sub-category with participants whose scores increased above the cut-off of 4 at least once during the programme was also formed.

Codes were brought together to form subcategories of similar content[226], under each of the timeline phases, grouping participants under the three EDE-Q trajectory trends. Finally, abstraction was used to form a general description of the topics under which sub-categories fell, which resulted in categories[228]. The process is described in Figure 4.1 below. Categories were also discussed with supervisors.

Finally, I adopted a critical realist ontology; codes forming may represent participants' opinions but are inevitably influenced by my positionality.

Figure 4.1 The qualitative content analysis process. Journal of Advanced Nursing, 62(1), 107-115, taken from Elo, S., & Kyngäs, H. (2008)[221]



4.4 Results

The baseline characteristics, as well as the mean weight loss, and change in EDE-Q and CIA scores for the sample of this qualitative analysis can be found in Table 4.1.

Table 4.1 Characteristics of the sample included in the qualitative analysis

	Whole sample Mean (SD), *n=22*	**Improving and stable EDE-Q scores** Mean (SD), *n= 11*	**Variable EDE-Q scores** Mean (SD), *n= 8*	**Worsening EDE-Q scores** Mean (SD), *n=3*
Age (years) at baseline	51.7 (8.2)	55.5 (4.2)	49.1 (11.1)	44.5 (0.1)
BMI (kg/m^2) at baseline	39.5 (7.5)	38.1 (5.2)	39.0 (8.7)	45.1 (11.2)
Gender (%)	30% male, 70% female	27% male, 73% female	40% male, 60% female	30% male, 70% female
EDE-Q global score at baseline	3.2 (0.3)	3.2 (0.2)	3.2 (0.3)	3.6 (0.5)
CIA score at baseline	21.5 (12.7)	16.6 (10.4)	23.4 (13)	34 (13.5)
EDE-Q change in scores from baseline	-0.7 (1.2)	-1.5 (0.8)	0.1 (0.7)	1.0 (0.4)
CIA change in scores from baseline	-10.8 (10.6)	-11.2 (11.7)	-10.8 (10.4)	-9 (9.9)
Weight change from baseline (kg)	-16.4 (9.9)	-20.5 (11.2)	-9.9 (1.0)	-13.6 (7.6)
Number of sessions recorded	5.5 (2.8)	6.3 (2.4)	4.0 (2.7)	6.3 (3.8)

In this sample, nine participants had improving EDE-Q scores and two participants had fairly stable EDE-Q scores, forming a group of eleven participants, whereas eight participants had scores with variable pattern. Finally, three participants experienced worsening EDE-Q scores. The average number of sessions per category was roughly similar between the group with improving and stable scores and the worsening scores; however, the average number of sessions recorded in the category with variable EDE-Q scores was smaller.

Codes are also presented chronologically during the phase of the programme when participants expressed them.

The three participants in the worsening EDE-Q group had quite distinct experiences in the programme. One completed the programme successfully and lost 19 kg and one lost a significant amount of weight in the first ~2 months but then stopped adhering to the programme and regained some of the lost weight, despite attending all sessions. The third participant followed

the programme for ~1.5 months and stopped engaging both with the intervention and the assessment.

Almost all participants in the group with improving EDE-Q scores adhered to the programme. This was evident by the average weight loss of 20.6 kg (SD 12.4), with only one participant having lost less than 10 kg (-3.7 kg) at 6 months, as they were the only ones not adherent to the programme. Another participant did not make use of all the sessions available due to a busy work schedule but still managed to follow the programme and lose weight. All participants completed the 6-month follow-up.

There were eight participants in the group with variable EDE-Q scores, of which six completed the study follow-up at 6 months. The average weight loss in this group was 9.9 kg (SD 1.0). Despite the absence of a variable pattern in the EDE-Q trajectory, three participants had eventually their scores reduced from baseline, and three had their scores increased at 6 months.

A sub-group of four participants who experienced scores above the pre-specified EDE-Q cut-off of 4 was formed; these were two participants from the group with the worsening scores and two participants were from the group with variable scores. The mean weight loss in this group was 11.3 kg (SD 4.3), with data available from all but one participant at 6 months.

The main categories and sub-categories throughout the stages of the programme can be found in Figure 4.2 below.

Figure 4.2. Main Categories and sub-categories. Differences are highlighted in grey.



4.4.1 Differences between the groups depending on EDE-Q trajectories

The main differences between groups were observed during the TDR phase.

4.4.1.1 Relationship with body and eating & challenges at TDR phase

Two of the 3 participants in the group with worsening scores experienced hunger in the TDR phase that, compared to the group who had improving/stable EDE-Q scores, were not able to manage as successfully and move past the difficult moments.

- Female, 44 y.o., worsening EDE-Q score, lost 4.5 kg: *"It's like, ridiculous. One day. I got really angry. I was shouting and swearing. But sort of, on that occasion, I actually calmed myself down. I had a soup and I was fine because I was just hungry."*

This led to extensive efforts to go back to the programme, but unsuccessfully; lapses became relapses.

Two participants in this group also reported their relationship with carbohydrates and sugar; one of them was able to overcome this with the help of the programme. Two participants reported eating in response to boredom and difficult emotions; as a result, when things became challenging during TDR, they found it especially hard to adhere to the programme.

- Male, 45 y.o., worsening EDE-Q score, lost 19 kg: *"Yeah, I think in the past I've had like a sugar addiction, so through sticking to this, it's been a big help turning it around"…"For 20 years I worked nights, so I was addicted to full sugar energy drinks, having like 4 a day."*
- Female, 44 y.o., worsening EDE-Q score, lost 4.5 kg: *"Certainly my response to feeling depressed, unhappy is generally to eat."*

All three participants in this group emphasised the mostly unhelpful nature of their environment, where they were very conscious of multiple cues for unhealthy foods.

- Female, 45 y.o., worsening EDE-Q score, lost 8 kg: *"I've just sat in the office today while everybody's been eating banana bread and I'm just like, I hate you all."*

  "But I mean, when you're out and about and then you know, you're constantly going out for dinner just trying to catch up with people and, you know, it just, it is difficult."

This was in contrast to a mostly helpful and supportive food environment experienced by the majority of participants in the group with the downward/stable EDE-Q trajectories.

- Female, 56 y.o, improving EDE-Q score, lost 22 kg: *"Everybody kind of knows about me and (the) family are really supportive"*

Many participants, regardless of the group they belonged to, reported occasionally "breaking" the principle of only consuming products while in the TDR phase by eating food; it seemed that in the group with improving/stable EDE-Q scores, this usually involved vegetables and was not perceived as a "failure".

In the group of eight participants with variable EDE-Q scores, half the participants reported issues with liking some of the products, which resulted in more challenges in adhering to the programme.

- Female, 43 y.o., variable EDE-Q score, lost 11 kg: *"I do feel tired and I'm getting to the stage that I'm not particularly looking forward to having the shakes and the soups, so they don't taste particularly nice. They all sort of taste the same."*

Half of the participants in this group also mentioned issues with non-adherence. Six participants found TDR challenging at some point in the three months due to different reasons; one had issues with different celebrations involving food, one had a very busy period at work, one struggled with hunger, one with their work schedule (working nights) and one had a non-supporting environment.

- Female, 43 y.o., variable EDE-Q score, lost 11 kg: *"My job is so mental…when I come home, instead of turning to that sandwich, which is an instant fix of food which, you know, I'm just ravenous, I should actually just (fall) asleep"*
- Male, 29 y.o., variable EDE-Q score, lost 9 kg*: "I've been doing like quite a lot of overtime (and long) shifts. So it was kind of at the back of my mind really to, I just wanted something like normal food."*

- Female, 52 y.o, variable EDE-Q score, lost 9 kg: *"I had a slice of birthday cake because, you know, my son made me a birthday cake. So I felt duty bound to have a slice of that."*
- Female, 45 y.o., worsening EDE-Q score, lost 8 kg*: "Except Halloween is on Tuesday next week and it's my favourite holiday so.."*

Only one participant reported remission of T2D as an important motivator in pursuing the programme. One participant who dropped off the intervention early on and eventually study follow-ups reported how rigid rules do not work for them and opted for some food consumption while on TDR. However, this resulted in feelings of guilt when attempting to monitor weight. Half of the participants proceeded to food re-introduction and 6/8 completed the follow-up at 6 months.

In the sub-group of participants who scored at least once above the cut-off of 4, no particular codes differentiating them from other participants occurred. Three out of four of them managed to lose significant amounts of weight and remained in the programme and the study till the end, despite the two experiencing issues with adherence, mainly due to their environment and way of living, as mentioned before.

Participants in the group with improving EDE-Q scores reported drawing motivation from seeing reductions in weight or experiencing other benefits (e.g. blood glucose levels) more frequently and profoundly than the other groups.

4.4.2 Similarities between the groups depending on EDE-Q trajectories

Apart from the differences described above, overall, similar experiences, burdens and facilitators were observed for all participants in the programme, regardless of how their EDE-Q scores evolved.

4.4.2.1 Relationship with body and eating

Most participants had tried various weight loss methods before; a handful of participants from all groups had also tried TDR before, however not in a structured programme with behavioural support, but on their own and with great difficulty.

- Female, 52 y.o., variable EDE-Q score, lost 9 kg*: "When I did a programme very similar to this, it very much was (that) you drink 4 litres of water a day, which seemed quite a lot and it was a lot."*
- Male, 55 y.o., improving EDE-Q score, lost 49 kg: *"When I tried it when I was in (a particular housing arrangement) last year, it sort of failed because of, probably with the diabetes. I started going for walks, I did the (commercial diet replacement programme) diet and I sort of started combining it with meals, probably didn't move too much and I ate too much, really, or too many carbs, I don't know, but I was really struggling, yeah."*

Most participants expressed notions that implied a sub-optimal relationship with their body, a non-intuitive way of eating, but also experiencing stigma from others. This was reasonable in the context of being recruited based on experiencing disordered eating. Some also reported being unable to rationalise portions when they have multipacks of readily available foods at home or eating to manage their emotions. Another participant reported the issue of cost, as nutrient-poor energy-dense food is often cheaper, or more easily available, compared to more healthful food.

- Male, 62 y.o., improving EDE-Q score, lost 19 kg: *"I wouldn't say there's any physical sight and changing when I'm looking at myself, I still look pretty disgusting. But that's my own fault. But I just feel no, I think if I can carry on, then it will improve how I look a little bit as well."*
- Female, 51 y.o., variable EDE-Q score, lost 5 kg: "*Sometimes I'm not hungry, I'll still eat."*
- Male, 45 y.o., worsening EDE-Q score, lost 19 kg: *"… Me being overweight affected my health in other ways, not just physically but mentally. Because I haven't had the confidence to go out and find (a) relationship."*

4.4.2.2 Living with T2D

Diabetes remission was a significant motivation for participants to successfully lose weight, due to the impact of its burden on their lives.

Some participants were aware of the impact of carbohydrates on their blood glucose, however, it wasn't always clear if their first concern was managing their blood glucose levels, or merely weight control. Often, some participants referred to this food group as the one they can't exercise portion control over, and some preferred trying to reduce their amounts, at least in principle. These notions were expressed by participants in all groups.

- Female, 56 y.o., improving EDE-Q score, lost 22 kg*: "I think the carbs are probably the thing that I kind of struggle in my head with the most because I think the Diabetic association are very clear about, you know, don't eat too many carbs and this kind of stuff."*
- Female, 53 y.o., improving EDE-Q score, lost 3.7 kg*: "I only ever have low-carb meals. Unless I need chips."*

Many participants, regardless of their group, reported how medication prescribed to manage diabetes had side effects that were a burden for them. Finally, a participant from the group with variable EDE-Q scores reported the amount of conflicting information around managing diabetes.

- Female, 56 y.o., improving EDE-Q score, lost 22 kg: *"The metformin was just horrible for me. I was miserable and my mood now is a lot better (that I stopped them)."*
- Female, 45 y.o., worsening EDE-Q score, lost 8 kg: *"I'm glad to be not taking the medication because I think it was causing me grief. One of the side effects is coughing and that was happening and everybody was looking at me like I was sick."*

4.4.2.3 Relationship with healthcare professionals

Diabetes was not the only condition most participants lived with; the majority were prescribed medication for hypertension and four participants in the intervention arm also had fibromyalgia. Only a small minority had T2D alone. Some participants lived with multi-morbidity which meant additional interactions with healthcare professionals, for diabetes and/or other conditions. Some participants reported the help they received from their healthcare provider to manage conditions co-existing with T2D had been sub-optimal unless they exaggerated their symptoms. In addition,

some people felt that the care they received was focused solely on medication, ignoring a more holistic approach to managing their condition, whereas stigma from a healthcare provider and reinforcement by healthcare professionals (HCPs) to lose weight to manage conditions beyond T2D were evident. Notions in this section were reported by participants in the improving scores group and in the group with variable EDE-Q scores.

- Male, 55 y.o., improving EDE-Q score, lost 49 kg: *"Doctors (…), they don't understand, if you don't make a nuisance of yourself. And always in the doctor, you (have to) complain. They don't know your real health or your real circumstances. So they just think you're healthy, don't they? If you don't complain about anything. "I don't know because I haven't seen you", that's what they've always said, if you haven't been in for a year or two."*
- Male, 58 y.o., improving EDE-Q score, lost 19 kg: *"I mentioned I'm on (x med) and I take quite a high doses as it is and the minute you speak to your GP about it, their answer is let's prescribe more medication, so they prescribe me the highest dose of (med y) a day. That's not the answer I don't think".*
- Male, 45 y.o., worsening EDE-Q score, lost 19 kg: *"He didn't have very good bedside manner as a doctor. He made me feel guilty for being sick."*
- Male, 60 y.o., variable EDE-Q score, lost 10 kg: *"Naturally, (the doctor) said you need to lose weight (for the knee, to avoid surgery and ensure healing), they said ideally it will be better to heal it naturally."*

4.4.2.4 Challenges (TDR phase)

In the first few weeks of the TDR phase, the main difficulty was adhering to a TDR in the context of an environment of food abundance and a social life revolving around eating. Participants reported challenges around cooking for the family or sharing mealtimes with the family or friends when they had planned holidays or special occasions, like birthdays and meeting friends, or around having food constantly around at work.

- Female, 46 y.o., variable EDE-Q score, lost 23 kg: *"I'm still struggling a bit. I still want food, you know, when my son and partner are eating, you know, like a sandwich and I'm still…I think the wanting food is getting more (intense) and I think I'm probably getting a bit bored of having shakes and things. So yeah, it's just a difficult stage, I think, maybe."*
- Male, 62 y.o., improving EDE-Q score, lost 19 kg: *"Food is everywhere; you go to people's houses, there's food. You go to shops, there's food."*

For some, another challenge of adhering to the programme was the poor taste of products while others commented on the lack of variety for them, given they might have not liked particular flavours.

- Female, 55 y.o., improving EDE-Q score, lost 24 kg*: "I don't know at the moment, it's all a bit weird trying to get back into it. You know what I mean? Going away I did think I was gonna be able to smash it, you know, but obviously it's like, my hands are tied, to be honest."*
- Female, 56 y.o., variable EDE-Q score, lost 11 kg*: "If there was more variety in it, it would be easier for people, but I'm okay with it and I'm sticking with it so I'm quite happy."*

Another challenge during the TDR phase was hunger. Despite their high-protein content which is more satiating than other macronutrients, products still only offer 800 kcal/day. Some participants experienced hunger during the TDR stage, either in the first two or second two weeks. The difference between groups, as mentioned above, was either the intensity or ability of participants to manage this successfully; participants in the group with improving EDE-Q scores were more likely to stick to the programme and manage hunger successfully compared to the other two groups.

- Female, 56 y.o., improving EDE-Q score, lost 22 kg*: "I do feel hungrier and I've not felt hungry at all since I've been doing this. Let's just say it's not starving hungry, it's not kind of, and it's certainly not enough to make me not carry on doing it."*

4.4.2.5 Facilitators of adherence (TDR phase)

Adherence was fostered through large initial weight losses, improved blood glucose and blood pressure control, as well as the prospect of remission. Some people simply reported that they were determined to succeed and make the most out of the programme.

- Female, 46 y.o., variable EDE-Q score, lost 23 kg: *"(Weight loss) kind of keeps me motivated to stick to it, really. I want to, like, get as much off as I can before we start introducing food back."*
- Female, 56 y.o., improving EDE-Q score, lost 22 kg: *"I know people are motivated by weight, but I'm quite motivated by my blood glucose levels coming down, bearing in mind I'm on no medication at all and I was on and I was on 2g of metformin before."*
- Female, 56 y.o., improving EDE-Q score, lost 22 kg: *"I'm not tied to a medication that devastated my day, it's been it's been so much nicer to be able to plan to go out and not have to worry about where I am."*
- Male, 58 y.o., improving EDE-Q score, lost 19 kg: *"You've just gotta get your head in the game, I think. Ohh, I'm the world's worst. I love food. But we're all responsible for what we put in our mouths. If you wanna succeed, then you know you've gotta put your head in the game, aren't you?"*

Many participants from the groups with improving and variable EDE-Q scores commented on the ease of the TDR phase, where they were not required to make choices about what to eat, other than what flavour of product to have. This was not mentioned by participants with worsening scores. Support in the programme both by the dietitian and their family environment was important in promoting adherence. One participant from the group with variable pattern in EDE-Q scores reported that the motivation in following the programme was that it is "based on science".

- Male, 29 y.o., variable EDE-Q score, lost 9 kg, dropped out of intervention: *"Personally, I prefer having these shakes, like a restricted diet, because I found in the past, if I've tried to follow like a diet…where you are eating normal food, you tend to overheat and then you'll lose the motivation, once you've had a few days where you've not stuck to what you're meant to be doing. So I personally find it easier to just to know right, today I've got four shakes and that's all."*
- Female, 56 y.o., improving EDE-Q score, lost 22 kg: *"I think having a lot of the choice taken away was one of the main things for me. So having that range, you know, it's a decent range of products that you can have … ohh that dread of what can you eat? Can I eat this can I eat that?[....] It's all pre-measured and diets in the past have never really been much like that. "*
- Female, 56 y.o., improving EDE-Q score, lost 22 kg: *"Thank you so much for your support. It's been invaluable. It's tough to do (it) on your own, definitely."*
- Female, 52 y.o., variable EDE-Q score, lost 9 kg: *"…this is a thought-out scientific plan, if you like. A (…) low-calorie diet looking at reversing your diabetes. So I kind of feel that, you know, people need to really think about that, (and) just do a considered approach."*

Participants experienced improvement in their physical and often in their mental health as they achieved weight loss, attributing it to both feeling the success they had achieved with hard work, but also having more energy, sleeping better (such as not waking up to urinate, a common symptom of high blood glucose), not taking medication and being able to engage in more activities of the daily life (e.g. climbing the stairs without shortness of breath).

- Male, 45 y.o., worsening EDE-Q score, lost 19 kg: *"I feel better than I was, and I'm not as depressed, I've got more energy"*

Finally, as participants navigated the programme and came in contact with healthcare professionals for other reasons, they reported receiving positive feedback on the results they had achieved through it and encouragement to continue.

- Male, 62 y.o., improving EDE-Q score, lost 19 kg: *"I actually saw my GP because I have to see them, and he's really pleased with me. And he was, he was chuffed, he said carry on and he was really supportive."*

4.4.2.6 Relationship with food and body (TDR phase)

Some participants in the group with improving EDE-Q scores found TDR gave them a chance to improve the way they eat and the quality of their diet compared to what they were used to, before embarking on the programme.

- Female, 54 y.o., improving EDE-Q score, lost 13 kg: "*I think it's helping to retrain my mind really to not pick up food. And I've started looking at different sort of recipes that are a bit healthier and thinking about what I'm gonna do at the end of this."*
- Male, 58 y.o., improving EDE-Q score, lost 19 kg: *"I am open that in the long term, it'll give me a more of a positive way of thinking about what food to eat and how I eat it."*

Some participants were concerned they would lose control of their eating, going back to eating during the stage of food re-introduction; this stage was perceived as difficult, compared the ease of the TDR phase. Participants observed changes in their weight, and subsequently in their bodies. These were topics they shared often during the consultations. Participants were usually quite content with observing changes in their regular clothes fitting loose, which some also reported as a motivation to continue.

- Female, 56 y.o., improving EDE-Q score, lost 22 kg*: "I know the thing is, it's about losing control, isn't it? Because, you know, once you kind of (lose control), it's difficult to get back on track, I think sometimes."*

- Female, 54 y.o., improving EDE-Q score, lost 13 kg: *"I can see the weight loss. I can see it coming off and I can get into some clothes that I couldn't before and all those little things motivate (me)."*

On the other hand, some participants had mixed feelings about their body changing, as they mentioned concerns about loose skin developing from significant weight loss in the future.

- Male, 55 y.o. improving EDE-Q score, lost 49 kg: *"The only thing I'm not looking forward to is the loose skin."*
- Female, 60 y.o., improving EDE-Q score, lost 13 kg: *"It's slowly going down, which is good because I don't want it to come off too fast, so I don't end up with the big skin flap on my belly."*

4.4.2.7 Transition to food re-introduction (TDR)

Many participants expressed their mixed feelings about the transition to food re-introduction early on in the TDR phase, particularly those for whom the TDR phase worked well. Some were understandably worried about transitioning to eating food again. For some, the worry was around maintaining the weight loss they achieved or even carrying on losing weight to achieve their weight loss goal.

- Female, 56 y.o., improving EDE-Q score, lost 22 kg: *"I do feel well. I think long term, if I'm anxious about anything is about how do I maintain (the weight loss) or even carry on.."*

For others, the concern was more specific about having to make choices about food again or about difficulty in exercising portion control. These notions were expressed pre-emptively before participants had the opportunity to embark on the next stage.

- Female, 56 y.o., improving EDE-Q score, lost 22 kg*: "I have to say, I've kind of got mixed feelings about it, if I'm honest, and I kind of flip between "Ohh it'll be nice to have some food" and I mean, I think I'm more worried about kind of losing a bit of control. Actually, this (TDR) has been OK. It's been very controlled and exactly what I'm having every day. No big issues."*

- Female, 45 y.o., worsening EDE-Q score, lost 8 kg: *"And I think the other thing is, like, the portion control, that's my biggest concern. You know, but I have noticed, like I said, I'm not eating as much as I used to, that's for sure, but yeah, that's something I need to really keep an eye on."*

4.4.2.8 Eating again (Food re-introduction)

Eating again, participants in this stage had the opportunity to reflect on including regular food in the diet. One of the subjects that arose in discussion with participants at this stage was around learning how to create tasty, healthy and low-calorie meals, in both cooking and experimenting with ingredients. Some, especially in the group with improving EDE-Q scores, channelled the enthusiasm of experimenting into looking for new recipes, ingredients and ways of cooking (e.g. air-frying).

- Female, 60 y.o., improving EDE-Q score, lost 13 kg: *"Well, that's what I've been trying to think and have bookmarked quite a lot of recipes online that are mostly vegetarian and vegan because I thought, well, you know, [I will experiment] a month with it because I'm not wanting that much more to eat vegetables."*

Some participants reflected on the challenge of eating again in terms of how helpful the TDR phase was, by allowing them a break from decision-making around eating. Some reported their reinstated difficulty in choosing food, in the context of the programme. Overall, the theme has been that generally, food re-introduction has been challenging for the ones who made it to this stage.

- Female, 56 y.o., improving EDE-Q score, lost 22 kg: *"Yeah, you need that [break]. It's almost like you have a break from everything and then you go back to looking at you, you get a bit of time to think."*

"Yeah, it didn't come as naturally [eating again] as I thought it was going to. It was a bit of a struggle initially, but over the last I'd say four days, I've really got back into enjoying cooking and thinking about what to have."

- Female, 56 y.o., improving EDE-Q score, lost 22 kg: *"Now I have to be honest and say I'm really struggling with finding food to eat."*

  "If it's been tougher than I anticipated, actually? It is. It took me a good couple of days, sort of good half a week to get into the habit of it. It's been fine. I've been enjoying it."

Some participants struggled to find a balance between simplicity and taste, while others felt that options, especially when going out, were limited for them to choose from.

- Female, 56 y.o., improving EDE-Q score, lost 22 kg: *"I think I've just gone for it, kind of so simple that actually it wasn't particularly nice."*
- Male, 45 y.o., worsening EDE-Q score, lost 19 kg: *"So the main thing for me is when you go out, no one caters for diabetics, no, like the ice cream van and that you can't get a sugar free lolly outside your house"*

Overall, some participants reported eating smaller portions at this stage, compared to what they used to before. Some also reflected on their upbringing and their relationship with food and the portions they have almost been conditioned to consume.

- Male, 58 y.o., improving EDE-Q score, lost 19 kg: *"I can't eat nowhere near where I used to because I get full too quick."*
- Female, 46 y.o., variable EDE-Q score, lost 23 kg: *"So yeah, I was quite proud, actually. 'Cause sometimes I think when I eat something, it can lead to just going crazy eating everything. But I didn't do that. So yeah, I was quite pleased."*

- Male, 58 y.o., improving EDE-Q score, lost 19 kg: *" I was always taught as a kid and I think that stayed with me that, you know, you do nothing good until you've got a clean plate. You can't eat your pudding unless you eat all your dinner. And that's with me. I think that's sort of ingrained from childhood. So I've always had to eat everything on my plate. You just have to try and turn that mindset from "don't need to eat everything". Because I don't need it all."*

Reviewing blood glucose and blood pressure during the programme, especially at this stage, meant that some participants had questions on how to interpret different readings, in relation to other factors (e.g. eating again, being sick, exercising, the impact of different types of carbohydrates on blood sugars, managing other dietary requirements). In relation to diabetes, some acquired knowledge they hadn't been offered before at the point of diagnosis, especially given this was the first time they actively measured their blood glucose levels. Participants responded positively to this new knowledge and understanding of their condition.

4.4.2.9 Weight loss, health and T2D (Food re-introduction)

In general, participants were content with their weight loss, whatever that was and regardless of whether they had achieved the expected ~1 kg per week during TDR; even those with less success, tried to remain positive and reflect on the alternative benefits achieved.

- Female, 55 y.o., improving EDE-Q score, lost 24 kg: *"I think, you know, it's coming along slowly. I didn't have any further great weight loss, you know compared to the first couple of weeks, but now I'm happy with [the] results I can see when I look at myself; when I've measured myself, you can see a difference definitely."*
- Female, 45 y.o., worsening EDE-Q score, lost 8 kg: *"So yeah, I have put a little bit of weight on, but blood sugars are still like 7.5, 7.8, around there, they've never really gone any higher. Lowest they've been is like 6. Clothes are still hanging off me, so that's good."*

Participants continued being content about the changes they made in their diet and the impact these had on their physical and mental health, as well as their energy and self-esteem. Some reiterated their motivation to continue with these changes and not undo the hard work they have put into the programme, especially given the significant benefits in the way they felt.

- Female, 62 y.o. variable EDE-Q score, lost 4 kg, dropped out of intervention*: "Yes, and it's only small [weight loss] but my indigestion hasn't been bad really, because I haven't been eating the food [that causes it to be bad]. So that's been quite good."*
- Female, 56 y.o., variable EDE-Q score, lost 11 kg*: "Feeling and measuring that I've lost a bit of weight has made me feel good because… I can do it, I've done it, and I know I can do it and I can keep doing it. So I suppose for self-esteem, it has given me a little boost. Mental-health wise, I mean, I've got stress and anxiety issues, but that's to do with illness. But yeah, losing the weight has definitely been a positive [thing]."*
- Female, 46 y.o., variable EDE-Q score, lost 23 kg*: "Oh yeah, much more energetic and just things like, my skin is better as well. Looks better and yeah, I just feel better overall."*
- Female, 56 y.o, improving EDE-Q score, lost 22kg*: "[Motivation] is stronger for me to continue it. And when I sort of look back at the way that I used to eat and that the life that I used to lead, it's not something I want to go back to and I know that the only way back to that would be just to go back to easy old habits."*

4.4.2.10 Reflections (End of programme)

At the end of the programme, participants were thankful for the support offered by the study dietitian. Some participants were able to reflect on old habits that contributed to weight regain after previous attempts to lose weight, habits contributing to higher weight, and what to potentially be mindful about, moving forward.

- Male, 45 y.o., worsening EDE-Q score, lost 19 kg: *"Having someone to talk to helped with positive mind frame to lose the weight."*

- Male, 55 y.o., improving EDE-Q score, lost 49 kg: *"[I have lost weight], I can't remember, a few times in my life, but then I've stopped it that way. I was exercising, and when you stop the exercise, and here comes winter, you become a couch potato, you're watching TV. Then, it's easy to get comfortable, to eat. So that's the hard thing for me, probably. But if I keep exercising and concentrating on the food, [I should be ok]."*

A lot of participants confirmed they were determined to maintain the changes they achieved, although understandably some expressed their mild concerns. Some mentioned looking into further support after the end of the programme, by either purchasing recipe books or searching for support programmes to maintain weight loss (from dietetic notes/diary). Finally, one participant mentioned they were concerned their healthcare provider might forget about them following being coded as with "diabetes remission" on their medical records. They did feel this is a conditional status and would still want to benefit from preventative measures for their overall health.

- Male, 58 y.o., improving EDE-Q score, lost 19 kg: *"A big motivation for me is, it's been a lot of hard work over the last six months to get to this stage; don't wanna undo that over the course of the next month or so."*
- Male, 58 y.o., improving EDE-Q score, lost 19 kg*: "They put me into remission now [on the system]. It is [amazing], but I'm just concerned that they're not gonna keep an eye on me, that's all. That's what I'm worried about, and I like my eyes to be checked and obviously my feet to be checked, even if it's once a year, just so (that) they keep an eye on me. [It] gave me that understanding. That, you know, they would forget about me. That's the impression I got."*

4.5 Discussion

This process evaluation was part of the ARIADNE non-inferiority trial and aimed to assess how and why scores of disordered eating changed throughout the programme. To do so, participants were grouped based on the trajectory of their EDE-Q scores.

Hunger management was identified as a key difference between groups, with those in the group with worsening EDE-Q scores reporting stronger feelings of hunger and being less able to manage it. They also reported eating in response to emotions and boredom, often lapsing from the programme and trying to go back to it unsuccessfully. Many participants in the group with variable EDE-Q scores reported issues with liking products, often resulting in non-adherence. Timing, in relation to a busy lifestyle or unhelpful environment, might have also played a role in non-adhering to the programme.

Regardless of the trajectories of their EDE-Q scores, participants expressed similar notions around their relationship with their body and eating, living with T2D and the relationship they had with healthcare professionals. The majority of participants experienced similar facilitators and barriers to adherence, whereas some experienced TDR as an opportunity to retrain their brain around food and welcomed the transition to food re-introduction with mixed feelings. Eating again came with various reflections on cooking skills, portions and what they were used to eating before, weight loss and their health status in relation to general health (physical and mental) and T2D. Finally, participants shared their reflections at the end of the programme and what they would take forward to ensure they maintain their hard-earned success.

4.5.1 Strengths

This study was the process evaluation of the ARIADNE non-inferiority randomised controlled trial described in Chapter 3. It involved recording dietetic sessions with the intervention participants, as they went through the TDR programme, transcribing them verbatim using AI to help build the basic content, which facilitated an iterative analysis. There is a benefit in the main researcher shaping the transcriptions used for analysis[229]. There is equally additional benefit in having the same researcher delivering the intervention and analysing qualitatively the recorded sessions; due to the rapport built with study participants, I have been able to develop a working relationship which I believe has helped people to open up and express their experiences throughout the programme. These recordings happened over the course of 6 months, in many cases, throughout

all the stages of the programme, allowing participants to elaborate on their thoughts; many participants repeated the same ideas more than once, giving credibility to the data. Finally, the sample size of 22 participants was more than enough to allow for coherent, clear and robust ideas to form, moving away from the notion of saturation[230].

4.5.2 Limitations

A limitation of this work is certainly the fact that I delivered the intervention to the study participants, being aware of their score trajectories throughout, as I had to observe them in case they increased beyond the safety cut-off set in the protocol. Reasonable concerns might arise around whether intervention elements differed between participants, in reaction to different score trajectories. This was discussed with my supervisors from the conceptualisation of the trial and it was indeed deemed as a potential risk. However, by reflecting on my positionality, I was able to mitigate some of the risks. I am not a trained eating disorders dietitian, so I am not equipped to be able to deal with increased disordered eating in a therapeutic form through the programme. The outcome was usually binary; either continue as usual or stop the intervention, after discussing with DMEC and supervisors. Indeed, regardless of score trajectories, if a participant couldn't continue successfully on the programme, problem-solving and alternatives were offered and the course of action was guided by participant preferences. Overall, I attempted to maintain a balance between the delivery of a pre-specified intervention and the need to conduct qualitative research; my questions revolved around how participants coped with adhering to the programme, any issues they faced and physical/mental health check-ins while navigating the stages of the interventions. Exploration of specific aspects of participants' experiences was opportunistic when participants felt they wanted to share and elaborate on them.

Similarly, as the dietitian delivering the session, I was asking participants for their consent to record the session to "capture their experience in their own words". As a result, participants were aware what they expressed would be used as part of the study results. Misrepresentations may

occur due to participants not expressing exactly how they feel in fear of thinking they might share things that are not what I wish to hear and will harm the study[231]. Indeed, a participant mentioned concerns on this (*"I don't wanna ruin your research, but it all, it all feels like it's going well").* I mitigated this risk by expressing to participants that I do not expect any specific results and that any experience is valuable and will help collect data to help people with T2D in the future. When I had concerns recording the conversation would have an impact on how much participants would feel confident to express, then I refrained from it. Writing down notes and having a reflexive diary ensured that I wouldn't miss valuable data, despite not recording. In addition, some participants did not continue in the intervention and stopped attending dietetic sessions; therefore, this might have introduced selection bias in the process evaluation, despite that the same participants might have completed the follow-ups online.

Another limitation lies in another aspect of the lack of blinding; analysis was conducted by one person, and in particular, the person delivering the intervention. I tried to reflect on my positionality to ensure I am aware of my own biases. Indeed, there is always a risk that different researchers might draw different conclusions from the same data[226]. Through meetings with my supervisors during the analysis, I discussed codes and the process evaluation, which helped mitigate this risk. Participants also completed questionnaires on well-being including the EDE-Q, as well as having a reflection diary and dietetic notes, which meant this worked as some way of triangulation, confirming data to an extent[232]. In addition, using content analysis, there is limited interpretation of what is said, therefore there is a reduced risk of extracting meanings that are not there.

The lack of blinding was purely due to lack of resources and time.

Finally, the lack of discussions around specific topics could be due to the methodology of collecting this body of qualitative data. I was led by participants and did not probe them about experiences they did not report. This could mean topics related to shame could have been missed in the delivery of the dietetic session. Interviewing participants with specific questions on what might

have not worked during the programme could reveal more sub-categories than the ones I was able to report in this study. This methodology was selected partly because of its strengths, and partly due to lack of resources and time.

4.5.3 Comparison with the literature, conclusions and implications

Previous trials which tested the effectiveness of TDR programmes on weight loss and diabetes remission have also conducted qualitative analyses around participant experiences and found some similar results to this work. Participants in the DiRECT study[192] expressed remission and medication side effects amongst the main motivations to try the programme. Participants equally expressed the impact of hunger on adherence, which was maintained using the available behavioural support. Interestingly, for some participants, a break during the TDR stage resulted in an interruption of the motivational momentum, resulting in weight loss and challenges to return to the programme, as it was observed mostly in participants with worsening or variable EDE-Q scores in the ARIADNE trial. Additionally, participants in the DiRECT trial also found that food re-introduction came with difficulty in letting go of the certainty of using TDR products and anxiety about relying on their own ability to maintain the results they had achieved. This was also described in the ARIADNE trial, regardless of EDE-Q trajectory. Some of the benefits reported in the DROPLET qualitative study[215] of people's experiences on the TDR programme were similarly observed in the ARIADNE study. Expectations around the TDR phase sometimes were worse than the reality of it, and hunger for the majority of participants (especially in the group with improving EDE-Q scores) was manageable. The ease of the programme was also one of the reasons boosting adherence to it. Participants who lost weight using the programme in both studies also mentioned feeling better and having more energy. DROPLET was unique in that the programme was delivered by lay coaches who had lost weight themselves. Support was equally praised in this study and the ARIADNE study. In the DROPLET study specifically, participants felt that the shared experience of weight loss improved the relationship they built with their coach. On the other hand, some participants in the ARIADNE study had a lot of questions around food and health/disease that

might have been challenging for a non-healthcare professional to address. Participants with these needs felt positive regarding the knowledge offered in the ARIADNE study; it is unclear how the absence of this option, by replacing a trained in nutrition healthcare professional with a lay coach, can affect different participants' experiences.

Literature on obesity, T2D, weight loss and disordered eating utilising qualitative methodology is somewhat scarce. In a qualitative study in people with symptoms of night eating syndrome[233], recruited from an NHS outpatient weight loss clinic, some similar themes were identified around their relationship with food. People in this study reported family attitudes (having to finish all food on the plate) as significant influences on their relationship with food, using food as a coping mechanism, and relying on food to regulate negative emotions; these were also reported, to an extent, in the ARIADNE study. However, the study did not report weight loss outcomes in relation to these themes. In another qualitative study[234] looking into the experience of living with binge eating disorder, some participants reported avoiding access to unhealthy food that triggers binge eating can work positively towards recovery whereas others identified having strict rules like "yes food" and "no food" negatively towards recovery. Indeed, in the ARIADNE study, notions broadly similar to these were mentioned; participants who completed the TDR phase successfully commented on the ease of the programme in helping them take a break from making choices around food. Another participant who dropped out of the intervention in the TDR stage mentioned that strict rules did not work for them, echoing the results of the previous trial.

In a qualitative study[235] with participants with prediabetes/T2D and binge eating disorder, participants reported long-standing efforts of dieting, even prior to the diagnosis of the former. In particular, sugar and other carbohydrates were mentioned as types of food limited in their weight loss efforts. Participants reported these attempts as repeating cycles of restriction leading to deprivation, followed by guilt/shame related to binge eating. Interestingly, this has been theorised as a mechanism of how dieting can lead to disordered eating, and in particular, binge eating[70]. In addition, participants described how the diagnosis of pre/T2D worked as a motivation

to change disordered eating behaviours, which however was not sustainable. Failures in controlling eating behaviour to manage diabetes were perceived more negatively, as the stakes were higher. Recommendations for diabetes management were sometimes perceived as rigid, resulting in black-and-white thinking and a higher risk for binge eating episodes to occur. Notably, similar notions were reported in the ARIADNE study, with diabetes remission, being a motivation to uptake the programme. It seems that the main difference between these two experiences lies in that given recommendations on changing one's diet are different to attending a structured programme, like TDR. The latter utilises behaviour change techniques to support participants to change their diet and achieve weight loss and it's far more effective in inducing weight loss compared to giving someone one-off advice. Indeed, participants in the ARIADNE study felt that experiencing weight loss and changes in blood glucose readings reiterated their motivation to continue the programme. Indeed, participants praised the support they received in succeeding in the programme, with some differentiating their experience on the programme to previous, unstructured attempts they made with similar programmes that didn't bring the results they observed this time.

This study attempted to identify similarities and differences in the experiences of people participating in a TDR programme according to their EDE-Q score trajectories. It appears to be that early success in the programme through experiencing less hunger, managing hunger and other emotions, and being in a supportive environment is reflected later on in improved disordered eating scores. This is likely due to better adherence to the programme. Supporting people to address these might increase the overall effectiveness of the programme. In summary, there was no evidence from the study presented in this chapter that participants were unduly distressed, even if scores worsened, as they were likely to discontinue the intervention.

Chapter 5. Discussion

5.1 Overview

In this chapter, I summarise the findings of my thesis, which has contributed new evidence to the impact of weight loss interventions on disordered eating. To do so, I systematically reviewed and meta-analysed the available literature, and utilised quantitative and qualitative methods to investigate the impact of a weight loss intervention used in the NHS on disordered eating in susceptible people with overweight/obesity and T2D. I discuss the findings of this body of work in the context of the existing literature, expand on the strengths and limitations, share my reflections and explore the clinical and research implications of this work.

5.2 Summary of thesis findings

In the introductory chapter (Chapter 1), I presented an overview of the available evidence on the intersection between overweight/obesity and T2D, one of its most common complications, and disordered eating. There has been a significant increase in the prevalence of obesity in the last two decades, and subsequently the prevalence of T2D. Weight loss offered with behavioural support in the context of a structured programme can help manage overweight/obesity and even offer people living with overweight/obesity and T2D the possibility of diabetes remission. However, there has also been a significant increase in the prevalence of eating disorders in the last 20 years, which are significantly associated with morbidity and mortality[58]. People with overweight/obesity and T2D often experience impaired mental health, so targeted weight loss initiatives for managing the physical health element of obesity and T2D often spark concerns in the public sphere and among HCPs, especially dietitians, that they would have inadvertent effects on mental health, through worsening of disordered eating. This was particularly evident recently, with the launch of the NHS Path to Remission, which aimed to offer the opportunity for diabetes remission through significant weight loss achieved via a TDR programme to everyone living with overweight/obesity and recently diagnosed T2D in England.

In Chapter 2, I summarised the available evidence on the impact of different weight loss programmes on disordered eating scores. I decided to include weight loss programmes alone or paired with medication licensed for weight loss and/or psychological interventions. Previous systematic reviews[101,236] excluded studies with interventions targeting disordered eating alongside weight loss, often experienced by people living with obesity (e.g. binge eating), or using weight loss pharmacotherapy, or were not able to conduct meta-analyses. The review included analyses from both single-arm and randomised trials. It showed that weight loss interventions produce moderate weight loss and are associated with statistically significant reductions in disordered eating scores. The results were consistent for all types of interventions and regardless of baseline disordered eating scores; they were however more profound in people with an eating disorder at baseline. I explored whether weight loss mediated the change in disordered eating, but there was no evidence of that in the meta-regression.

The review identified only two interventions using low-calorie programmes like TDR and I was not able to conduct a sub-group analysis of them. TDR is a more "rigid" weight loss programme compared to more typical food-based hypo-energetic diets and is now being used widely in England to help people with overweight/obesity and T2D to offer them the possibility of diabetes remission[199]. To respond to the concerns of eating disorder charities, healthcare professionals and some members of the public that this programme may cause or exacerbate eating disorders, I conducted the ARIADNE trial, presented in Chapter 3. This was a non-inferiority randomised controlled trial utilising mixed methods to assess if there was evidence that a programme similar to the NHS Path to Remission had any greater adverse effect on disordered eating scores compared to usual care, in people living with overweight/obesity and T2D. I recruited 56 participants using social media advertisements and randomised them 1:1 to receive the TDR programme or continue with care as usual. I created the resources of the programme and delivered the programme to participants in the intervention arm. Participants in both groups completed follow-ups online at 4, 12, 16 and 24 weeks (end of the programme), which included

questionnaires on disordered eating, psychosocial impairment, depressive symptoms and diabetes distress. The primary outcome was the disordered eating score change at 24 weeks. At the end of the intervention, participants in the intervention arm had lost significant amounts of weight. There was evidence that scores for disordered eating and impairment from it had improved significantly compared to usual care. The same was also observed for depressive symptoms and diabetes distress symptoms. The TDR programme did not increase scores of disordered eating and impairment from it, as well as all disordered eating subscale scores, more than usual care. The only exception was the sub-scale of restraint, for which there was no evidence of non-inferiority. The results of non-inferiority were confirmed both in the intention-to-treat and the per-protocol populations. Furthermore, the intervention was deemed superior in reducing disordered eating and its impairment, compared to usual care.

In Chapter 4, I attempted to understand why and how disordered eating scores changed, by identifying similarities and differences in the experiences of people participating in the TDR programme according to their disordered eating score trajectories. For a large proportion of people randomised to the TDR programme, participants lost weight successfully and disordered eating reduced; a small minority reported an increase in their scores. The latter were more likely to struggle with hunger during the TDR phase and have an environment that added challenges to their attempt to lose weight and to feel the urge to eat in response to difficult emotions. As a result, lapses from the programme became relapses. Some participants eventually stopped the programme, often early on. Participants who experienced reduced or stable disordered eating scores expressed that the success of the programme reinforced their motivation. All participants who lost weight expressed feeling anxious to not go back to old habits and undo their hard-earned results, were grateful for the support received and were happy with both weight reduction and better diabetes management. Some also achieved diabetes remission, which was described as having been a significant motivation for programme uptake.

5.3 Strengths and limitations

5.3.1 Strengths

A strength of this work was the use of mixed methods. Across my studies, I drew from learnings from a systematic review, an RCT and a qualitative study. Results on disordered eating reduction after weight loss programmes were consistent across methodologies providing confidence in the robustness of the conclusion. This is particularly reassuring given that this body of work also attempts to answer an important and current public health concern on the potential harms of weight loss on disordered eating voiced by multiple stakeholders, from charities and healthcare professionals to patients and the public.

5.3.2 Limitations

A limitation in the ARIADNE study is reflected in the sample not being representative of the English population, mainly due to the small size and the predominantly White ethnicity; it was though representative across socioeconomic strata and with a higher proportion of male participants than usually present in weight loss trials. It is established that people of Asian, Chinese, Black African and Black Caribbean heritage are 2-4 times more likely to have diabetes than people of White heritage[18], but the results of the ARIADNE study might not be generalisable to that group. One of the reasons why the study did not include as many people with this background was that at screening, often these participants were not eligible due to complications (e.g. renal disease) or had worse diabetes control, requiring non-eligible medication like insulin, despite only being within 6 years of diagnosis. Additionally, another limitation of this work was that I was the dietitian delivering the intervention; I was not blinded to changes in self-reported scores and also recorded sessions and conducted the analysis of the qualitative study. This might have inevitably inserted bias in the interpretation of the results, despite efforts to minimise this. This was done due to a lack of resources and time, and also as a learning opportunity.

5.4 Implications for research, policy, and practice

This research addressed an important and relevant research question. It provides consistent evidence that weight loss programmes, even rigid ones like TDR with behavioural support, do not, on average, worsen disordered eating behaviours and in fact, are associated with a reduction in disordered eating symptoms and psychopathology compared to usual/minimal care. The next steps beyond this work involve expanding the ARIADNE trial, using resources offered by NHS England, to test whether small risks might be detected. This will translate into a larger sample, with active efforts to ensure more representation in terms of ethnicity, which will also receive the intervention through the regular channels it is delivered in the NHS. This will hopefully increase the generalisability of the results, offering more reassurance and adding to the evidence base of the evaluation of this service.

Reflecting on how the programme in the ARIADNE study was theorised to act on disordered eating, the direction of effect for the majority of participants was the opposite of the anticipated. In cognitive behavioural theory[70], eating disorders or disordered eating result from overvaluation of the control of eating weight and or shape, leading to body dissatisfaction that prompts an individual to impose rigid rules to achieve a certain weight or shape. Efforts to adhere to extreme and highly specific rules can break down, for example at times of negative emotion, and temporary abandonment of the rules, leading to overeating and lowering self-esteem, leading to even more rigid rule formation. Contrary to the theory, the rigid TDR programme advising people to abide by strict rules led to successful weight loss, improved confidence in their abilities to have structure in their eating and avoid episodes of overeating. The reasons for these remain to be elucidated in future research but may include increased self-esteem and improved body image, as they were observing the weight loss and feeling positive that they achieved their goals. Most participants who experienced an improvement in disordered eating did have some minor lapses but were able to continue the programme, reflecting on them and using problem-solving and utilising the support available, which they praised. This could have been an indirect observation

of flexible restraint, which has been associated with the reduction in binge eating and successful weight loss[237]. However, different types of restraint are not measured separately with the EDE-Q. For the small number of participants who experienced worsening disordered eating scores and participated in the qualitative study, lapses from the programme were usually reported to be due to environmental factors, hunger and eating in response to emotions, and eventually became relapses. Indeed, according to the cognitive behavioural theory of eating disorders, it is relapsing that maintains people's beliefs that they cannot maintain self-control, as manifested in control over their eating, weight, and shape and these beliefs promote binges. Furthermore, relapses happen commonly in response to acute changes in mood, where low mood, for example, reduces the will to maintain restraint. According to the Dual-Pathway model[82], body dissatisfaction fosters dieting and negative affect, which increase the risk of disordered eating, as eating provides comfort from negative emotions.

A limitation of the cognitive behavioural theory is that it was initially proposed to explain the maintenance of bulimia nervosa, and subsequently extended to anorexia nervosa and their variants, with authors arguing that many eating disorders tend to be maintained by similar psychopathological processes. More recently, the model has been adopted and enriched, incorporating obesity in it and integrating mechanisms recognised to maintain binge eating[238], which is more prevalent in this population. Therefore, it now specifically categorises inflexible restraint as the factor maintaining the disorder. It also incorporates life events and their associated mood changes as a factor contributing to the maintenance of disordered eating, which was explicitly mentioned by participants who experienced worsening disordered eating in the ARIADNE study. It is unclear if there were also other reasons why a small minority of people experienced worsening in their disordered eating versus the rest of the participants who saw their disordered eating improving. In the expansion of the trial which will aim to recruit a larger sample, further sub-group and qualitative analyses might help shed some light on specific factors determining why some participants experience worsening disordered eating, in order to integrate

better support in the programme for all. It might be useful to investigate whether different participants experienced hunger differently as a reason for non-adherence to the programme. Equally, if a less supporting environment is found to be behind non-adherence and subsequently disordered eating, a feature in the programme could be developed to foster a more supportive environment.

The most common notion proposed by critics of the NHS Path to Remission is the lack of screening for eating disorders. However, screening adds significant cost to the healthcare system and the time from referral to initiating the programme may reduce access to these intervention. The systematic review presented in Chapter 2 showed that the most profound reduction in disordered eating following undertaking a weight loss programme was observed in people with an eating disorder/high risk for disordered eating at baseline. This might reflect regression to the mean or a true estimate. In either case, it implies that screening is unnecessary, and if anything, might deprive people of interventions that they could benefit from. Screening for people who would not benefit or might be harmed could be an option in theory, if certain characteristics were predicting these participants would be harmed from the intervention. An older study[239] attempted to identify baseline characteristics of people who would meet the diagnostic criteria for binge eating disorder after following a similar low-energy programme to the ARIADNE study. The study included participants with obesity and either no baseline binge eating, sub-clinical binge eating and a diagnosis of BED at baseline. The study failed to identify predictors; once again, over half of participants with BED followed the programme, lost significant amounts of weight and stopped meeting the criteria for it. Three participants (10%) without binge eating at baseline met the criteria for BED at 1 year. The authors also found that weight gain was associated with a diagnosis of BED at 1 year. A limitation of this study was the lack of control, which could have better explained some of the findings. Evidence on the incidence of BED is scarce[240] and the small number of participants could have developed the disorder independently of the programme, eventually. Further research on whether certain participant characteristics could influence the outcome,

apart from baseline disordered eating status, would be useful. There is a relevant individual participant data meta-analysis on the subject underway[101]. The team is collecting individual data on baseline characteristics like eating disorder history, prior weight loss attempts, mental health comorbidity, personality traits, psychosocial health and eating behaviours, amongst others[101]. If screening were to be implemented, it is also unclear what could happen to people living with overweight/obesity and T2D or other conditions, who are keen to undertake a programme proven to manage their condition and are screened out of it. If no alternatives exist for them, people could still impose their own highly specific and strict rules and could fail to adhere to them, leading to further despair and potentially weight cycling and/or worsening disordered eating.

The longer-term impact of weight loss programmes on disordered eating remains a valid concern. In the systematic review, the median long-term follow-up was only 9.5 months from baseline. The ARIADNE study included two longer-term, 1-year and 2-year follow-ups, the results of which are beyond the scope of this DPhil and will be reported separately. Prospective long-term data will help shed light on the impact of TDR long after the intervention completion when some weight regain will have likely occurred. The 3-year results of the DROPLET study[241] and the 5-year results of the DiRECT study[38] showed that weight regain happens and, in the latter, only a minority of patients maintained remission at 5 years. There is lack of evidence regarding how disordered eating and mental health evolve in people who regain weight and might cease to be in remission. Older theories support that chronic dieting might predispose individuals to disordered eating[90,91], so the cumulative effect of dieting to lose the weight regained on disordered eating is something to be investigated. However, a recent systematic review[99] found that despite weight regain after weight loss programmes, there was no evidence of worsening mental health outcomes and even some evidence that they might improve some mental health aspects at and after programme end. As with all treatments, there might be a small number of participants who will not benefit and might even experience worsening disordered eating. Trials are designed to assess the impact of treatment on average in a population; when there are small minorities with scores far from the

average, their contribution to assessing the outcome is diluted. Reflecting on the results of the trial, 20% of participants in the intervention arm did not complete the 6-month follow-up and 20% proportion of participants who did, experienced worsening of their disordered eating. In terms of statistics, multiple approaches were taken to account for missing data, including a worst-case scenario imputation. There is no way of knowing what happened to people who did not complete the follow-up with absolute certainty. The worst-case scenario imputation assumed significant worsening in their scores and the outcome did not change, providing reassurance in the conclusions I have drawn. In the qualitative analysis, participants who experienced worsening of their disordered eating did not report feeling that the programme harmed them, but it might be that they could have felt like they could not report this to the interventionist. Future research could address some of these biases, by employing an independent researcher to conduct qualitative interviews. It is still possible, however, that participants might feel obliged to not disclose the full truth. Likewise, there will still be missing data, with no ideal way of handling them. In designing policy, the focus remains on the population on average, and this body of work shows that the programme can be offered to the population with reassurance that it does not cause harm to most people.

It is still important to design services that are capable of safeguarding the small minority that might not benefit or could be harmed by the treatments available and then offer integrated alternatives to them. In clinical practice, if participants stop engaging with the programme or self-report symptoms of impaired mental health to the coaches, a conversation about alternative services could be useful. This presupposes that the system is agile enough to identify participants who are not benefiting or harmed early enough and that alternatives are available to signpost these participants to. In the ARIADNE qualitative study, participants often expressed certain expectations about the programme. In most cases, they felt the programme was easier to follow than expected and quite effective. Moving forward, in the implementation of the programme, discussing expectations with participants might be useful, to mitigate the risk of participants

experiencing failure of the programme as their failure to adhere to it. From the qualitative study, it was often clear in the first few months which participants were able to adhere adequately and benefit from it, avoiding the unnecessary vicious circle of failing to adhere and trying to restart TDR, to no avail.

Remission is important to people living with T2D[30] and for those who also live with overweight/obesity, significant weight loss is a predominant way to achieve it[242]. TDR is one way to achieve significant weight loss[243], but it might not be for everybody, regardless of the reassurance that is not associated with disordered eating. Diabetes UK and the National Institute for Health Research (NIHR) are funding new research on supporting more people with overweight/obesity and newly diagnosed T2D to lose weight and have an opportunity to achieve diabetes remission. The New Remission Care Pathway: Diabetes Adaptive Weight Management Network (NEWDawn) study[244] will recruit participants to participate in a TDR programme as a first-line approach to weight loss and diabetes remission. If the programme is found not to be working for them early on, in agreement with their coach, they will be switched to up to four alternative interventions. These will include a food-based low-energy diet, local tier-3 weight loss services or a digital weight loss programme. The approach in switching therapeutic approaches is viewed and communicated to participants as a failure in the programme to meet their needs, rather than the participant's failure. This might be an important mitigating factor in avoiding potential worsening of disordered eating, as an individual's perceived failure to adhere to strict dietary rules like the ones described in TDR might perpetuate the vicious cycle of maintaining the psychopathology of disordered eating described in the cognitive behavioural theory[245]. In this case, it would just be the programme's failure.

The NEWDawn trial will offer, amongst others, a food-based low-energy low-carbohydrate programme found to have reduced weight by 7.5 kg compared to control and a reduction in HbA1c of −15.7 mmol/mol at 12 weeks[246], and is now investigated in a trial on remission[247]. Low carbohydrate interventions delivered in primary care have been considered an option for diabetes

remission and weight loss[248,249]. However, the debate on their efficacy in the management of T2D continues[250]. Other weight loss interventions might also be a viable alternative for those who wish to pursue them instead; an intensive lifestyle intervention was compared against a diabetes support and education control condition in the Look Ahead study[251]. Participants in the intervention arm lost 7.9% of their baseline weight and 11.5% had achieved remission at 12 months. Results were much more modest compared to the results observed in the DiRECT trial but potentially proportionate to the weight loss and type of intervention. To conclude, there are different approaches to weight loss and diabetes remission, some more successful than others in terms of potential to induce remission, with more research underway. What is missing and what the NEWDawn study might advocate for is the integration of the variable options in a more streamlined pathway, to avoid frustration and delays participants might experience otherwise.

There is also a group of patients who might not wish to pursue weight loss at all. Approaches like Health at Every Size™[252], based on intuitive eating principles and body neutrality, could be an alternative. Health at Every Size™ encourages participants to accept their body, eat and move intuitively, mindfully, or based on hunger/fullness cues, and has gained more momentum in the last 20 years[253]. Health at Every Size™ hypothesises that weight loss approaches might harm mental health and are unsustainable due to weight regain, so they adopt an approach targeted at psychological wellbeing[254,255]. Despite their promising prospects, they are often researched in short-term pre-post studies mainly including White females living with overweight and class I obesity, rather than class II and III (more severe obesity)[253], limiting the generalisability of the results. A systematic review on the impact of Health at Every Size™ interventions versus any control comparator on health-related outcomes in people living with overweight/obesity[256] found limited evidence of improvements in cardiovascular status, eating behaviours, quality of life and psychological well-being. However, a meta-analysis was not conducted. A more recent systematic review[257], published in 2024, attempted to bridge this gap and updated the previous systematic review, this time identifying enough studies to conduct a meta-analysis. The team found a

significant reduction in susceptibility to hunger in the weight-neutral intervention compared to any control, but no significant difference between the impact of weight-neutral interventions and control groups for all other outcomes: anthropometric, psychological or cardiometabolic. A 2020 systematic review[258] compared weight-neutral interventions versus weight-centric approaches specifically, on physical and psychological outcomes and identified 10 eligible studies. Meta-analyses were conducted with only two studies per category, for each of the disordered eating questionnaires used. The study concluded that there was a statistically significant reduction only in symptoms of bulimia in the subscales of the eating disorder inventory, associated with weight-neutral interventions compared to weight-loss interventions. There was no difference in binge eating, self-esteem, depression and quality of life between the two types of interventions. It currently seems that there is not enough evidence to support weight-neutral interventions over weight-loss interventions, both in physical and psychological outcomes in the population. Given the lack of evidence of harm, people who do not wish to undertake a weight loss programme could opt for a weight-neutral one. However, more compelling evidence of benefits is required before weight-neutral interventions can be offered within the healthcare system. It is imperative that whatever options are available to people living with obesity, the system offering these free of weight discrimination and fat-phobia, as they have severe implications, including avoiding accessing healthcare all together[259].

5.5 Personal reflections

Finally, there are some personal reflections and learnings I acquired in the process of conducting this DPhil, that despite not being reflected in the data per se, I think are important to describe, as they complement the findings of this body of studies and might help guide future research.

This work stemmed from my interest in what drives behavioural change, how evidence-based and effective our recommendations are as dietitians, and how we can ensure a holistic improvement in the outcomes of service users, without “fixing” one thing to the detriment of another. I found that NHS systems are sometimes equipped to deal with only one problem at a time, streamlining

people through specialities, with conditions and their impact often overlapping and systems unable to cater to more complex needs. For example, in a weight management clinic, there might be patients with disordered eating, with a service only commissioned and/or capable of dealing with the weight loss alone. It might therefore feel logical to exclude patients with disordered eating when they have no alternative service to turn to.

As healthcare professionals, we have a moral obligation to reflect on our biases around weight and ensure we work on abolishing them. I started this research as a dietitian curious to find out if offering weight loss can harm people more than it can help them. There is a rising trend of colleagues working in nutrition and dietetics attending intuitive-eating[260] courses and discussing a more weight-inclusive approach[261] in their consultations with patients, and I was a supporter of the anti-diet movement myself. After all, I thought it came hand in hand with opposing weight discrimination. This meant that sometimes we had to consider whether to discourage participants from pursuing weight loss for issues they might experience and were seen for in the dietetic clinic. My thinking changed after a specific encounter with a patient. A colleague had recommended intuitive eating and moving away from weight loss for them; weight loss was not contraindicated per se, but the colleague preferred offering this option. When I picked up the clinic from the previous consultation and read the notes, I asked the patient how it went. The patient was adamant that intuitive eating was not for them and they never wanted it in the first place; after all, they had a condition and wanted to lose weight to better control it, as this was a source of concern for them. This was the point that I realised that weight loss might not be for everyone, but it might be for some. My duty as a healthcare professional is to provide patients with the best, at the time, available evidence for them to make an informed decision, based on their personal experience and beliefs. For some, losing weight is important for valid reasons like diabetes remission, less joint pain and more energy. It was quite evident from the early stages of the trial that people living with obesity and T2D randomised to the control group, even in the context of a trial and knowing they could not get the programme, were left feeling utterly helpless and with

no hope for better control of their diabetes. Reading about the prospect of stopping diabetes medication, in the context of side effects and their burden to live with, they wanted to give remission a chance. In a conference on diabetes, I attended during my DPhil, dietitians in a weight management service presented their work using the EDE-Q to exclude people from the TDR in fear of eating disorders. However, reflecting on the results of this body of work, it seemed that they probably excluded people with complex needs who, at least some of them, might have benefited from the programme.

It is also not possible to always predict how well patients do in treatment and if their priorities change along the way. The same patient might find that what they thought would be useful to pursue as a treatment is actually not helpful to them anymore and they would benefit from an alternative. So how do we build evidence-based healthcare services, offer highly beneficial therapies and minimise harm?

Combining the learning from this body of work and my reflections along the way, I conclude that to create these services, it's important to draw evidence from different methodologies; quantitative systematic reviews and meta-analyses, randomised controlled trials, as well as qualitative studies. The strengths of one methodology can account for the limitations of another. However, this should not be considered the end of it. It's not always possible to predict how these services evolve and continuous evaluation is equally important, especially if there is not enough time to combine data to inform the design of a service before its implementation. This body of work shows that the results were different than originally anticipated, offering some reassurance in the roll-out of the NHS Path to Remission programme. They do not replace service evaluation though; they complement its direction.

Equally, an agile system that could signpost participants to alternatives, without another lengthy waitlist, would be the best direction to improve the current availability of services. Healthcare professionals working in it would ideally have the skills to have frank conversations with their patients on all the available alternatives.

5.6 Conclusion

The research presented in this thesis has helped advance the field of the interaction between obesity and disordered eating in the context of using weight loss treatments in the management of obesity and its complications, like T2D. I conclude that despite being thought to be detrimental to disordered eating, weight loss programmes in general are associated with reductions in disordered eating, regardless of baseline status, at least in the short-term. In people living with overweight/obesity, disordered eating and T2D specifically, a programme similar to the NHS T2D Path to Remission produces significant weight loss and is not only non-inferior but also superior to usual care in terms of disordered eating.

The findings have significant policy implications, as they offer reassurance to relevant stakeholders of the NHS T2D Path to Remission that the physical effects of the programme are likely to occur without the concern of psychological adverse effects. I hope this thesis contributes to the available knowledge in the field and helps signpost the direction of future research and contribute to the safety of patients.

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Appendices

Appendix 2.1 Systematic Review- Tables and figures

Table A2.1 Risk of bias table, RCTs

Study	**Randomisation process**	**Effect pf assignment to intervention**	**Effect of adhering to intervention**	**Missing outcome data**	**Measurement of outcome bias**	**Selection bias**	**Total**
Berk et al., 2018 [122]	?	-	?	+	+	+	-
Grilo et al., 2005 [123]	+	+	+	+	+	+	+
Wilfley et al., 2002 [124]	?	+	+	+	+	+	?
Carels et al., 2021 [127]	?	?	?	-	+	?	-
Chao et al., 2019 [128]	?	?	?	+	+	+	?
da Luz et al., 2017 [129]	+	+	?	?	+	+	?
Mensinger et al., 2016 [131]	?	+	-	?	+	+	-
DiMarco et al., 2009 [132]	-	?	-	-	+	?	-
Grilo et al., 2021 [133]	+	?	?	?	+	+	?
Grilo et al., 2005 [134]	+	+	+	+	+	+	+
Dassen et al., 2018 [135]	?	+	+	?	+	+	?
Grilo et al., 2013 [136]	+	+	+	+	+	+	+
Grilo et al., 2020 [138]	+	+	?	+	+	?	?
Loader et al., 2013 [139]	+	?	?	?	+	?	?
Nauta et al., 2000 [140]	?	+	+	+	+	?	?
Grilo et al., 2011 [141]	+	+	+	+	+	+	+
Masheb et al., 2011 [142]	+	+	+	+	+	+	+
Munsch et al., 2007 [143]	-	+	?	-	-	+	-

Preuss et al. 2017 [145]	?	?	+	+	+	+	?
Ramirez et al., 2001 [146]	-	-	+	?	+	-	-
Rock et al., 2010 [147]	+	?	+	+	?	+	?
Barnes et al., 2017 [148]	?	+	+	?	+	+	?
Moss et al., 2017 [116]	?	?	+	+	+	+	?
Werrij et al., 2008 [150]	?	?	?	+	+	+	?
Wilson et al., 2010 [151]	+	+	+	-	+	+	-

Table A2.2 Risk of bias table, observational studies

Study	**Newcastle-Ottawa scale score**
Calugi et al., 2016 [125]	6
Carbone et al., 2021 [126]	7
DalleGrave et al., 2020 [130]	4
Abiles et al., 2013 [137]	4
Pataky et al., 2018 [144]	4
Barnes et al., 2018 [149]	5

Figure A2.1. Funnel plot of single arm trial publications in the end of the intervention

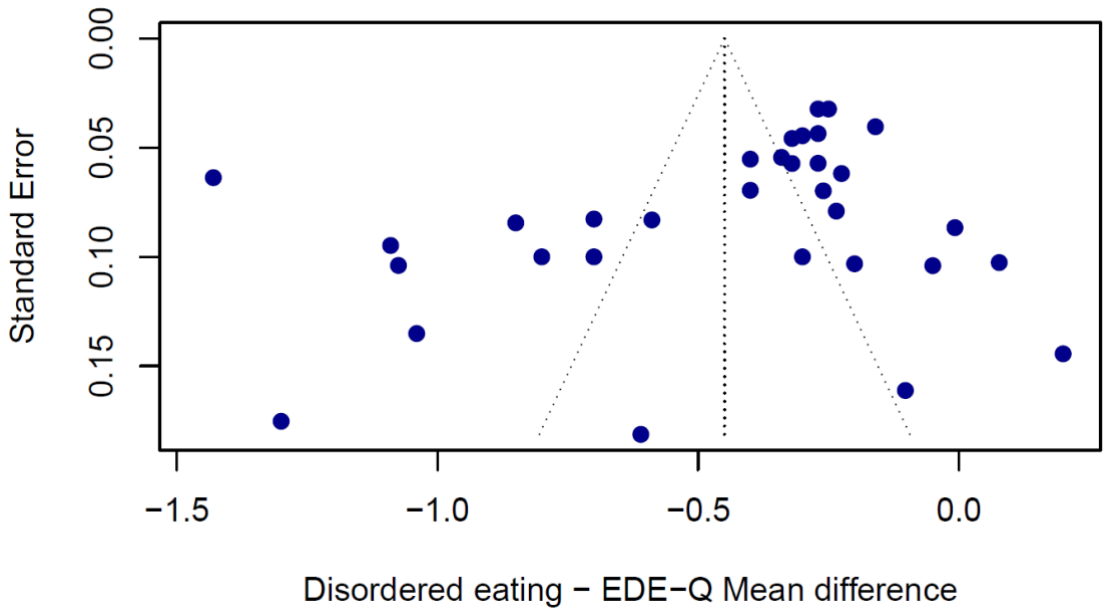
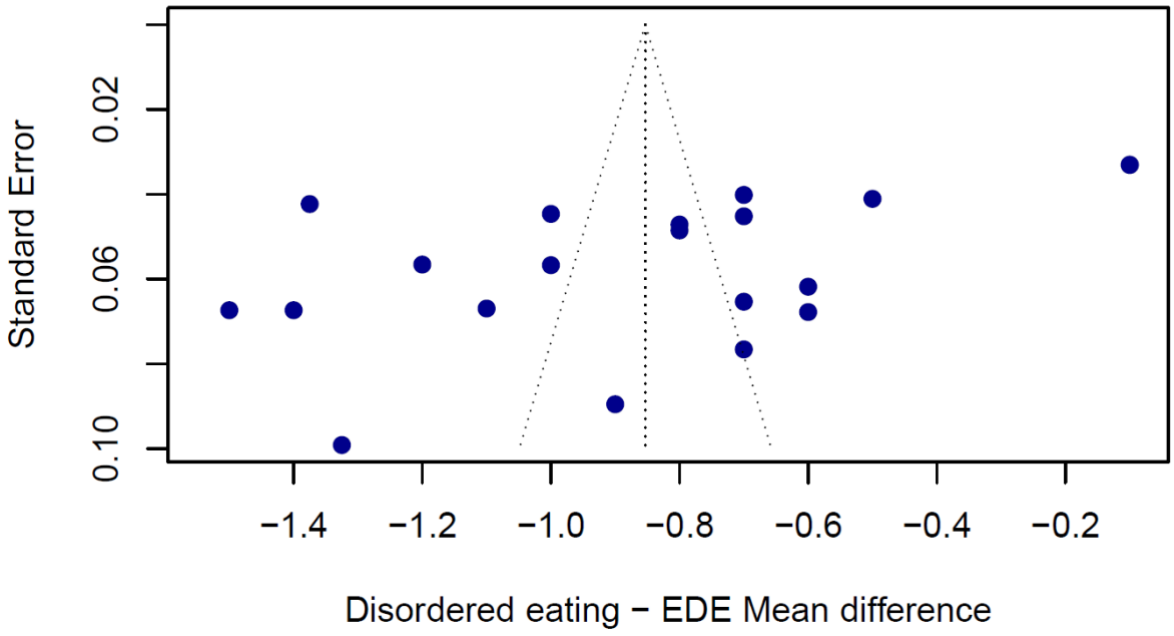


Figure A2.2. Funnel plot of single arm trial publications in the end of the intervention



Appendix 2.2. Systematic review- Search strategy

EMBASE search strategy (16.05.2022)

Embase 1974 to present

1 obesity/ or morbid obesity/ or abdominal obesity/ 510645
2 (overweight or over weight or overeat* or over eat* or overfeed* or over feed*).ti,ab. 126953
3 obes*.ti,ab. 507081
4 1 or 2 or 3 659127
5 weight loss program/ 2875
6 body weight loss/ and (modific* or therap* or intervention* or strateg* or program* or management or scheme* or group* or club? or pathway* or service?).ti,ab. 38268
7 ((weight adj1 (los* or reduc* or manag*)) and (modific* or therap* or intervention* or strateg* or program* or management or scheme* or group* or club? or pathway* or service?)).ti,ab. 119546
8 obesity/dt, pc, th or morbid obesity/dt, pc, th or abdominal obesity/dt, pc, th 44994
9 diet restriction/ or caloric restriction/ or diet therapy/ or exp low calorie diet/ or low fat diet/ or high-protein low-carbohydrate diet/ 175521
10 (diets or dieting).ti,ab. 123863
11 ((low calorie* or low energy or hypocaloric or calorie control* or low fat* or fat control* or low carbohydrate* or carbohydrate control*) adj2 diet*).ti,ab. 16509
12 (health* adj1 eating).ti,ab. 13219
13 (diet* adj2 (modific* or therap* or intervention* or strateg* or program* or management or scheme* or group* or club?)).ti,ab. 66032
14 (nutrition* adj2 (modific* or therap* or intervention* or strateg* or program* or management or scheme*)).ti,ab. 38211
15 (Weight Watchers or slimming world or lighterlife or lighter life or jenny craig or diet chef or nutrisystem or slimfast or slim fast or medifast or optifast or modifast or nutrilett or hmr or cambridge diet).ti,ab. 2458
16 (commercial* adj2 (program* or intervention? or weight loss or diet?)).ti,ab. 3551
17 (meal? adj2 replace*).ti,ab. 1224
18 ((preprepared or pre-prepared or prepared) adj2 (meal? or food? or snack? or portion?)).ti,ab. 2339
19 ((prepack* or pre-pack*) adj2 (meal? or food? or snack? or portion?)).ti,ab. 303
20 (eating plan? or meal plan* or planned meal? or planned menu?).ti,ab. 1364
21 (portion control* adj2 (diet? or meal? or food? or weight loss)).ti,ab. 108
22 (liquid adj2 (diet? or meal? or food?)).ti,ab. 11074
23 (replace* adj (snack? or drink? or food? or liquid?)).ti,ab. 139
24 shake?.ti,ab. 16202
25 (isoenergetic adj (diet? or food? or meal?)).ti,ab. 605
26 cognitive behavioral therapy/ or behavior therapy/ or cognitive therapy/ or counseling/ 167302
27 (((behavio* or cognitive) adj2 therap*) or cbt).ti,ab. 53453
28 ((chang* or modif*) adj2 (lifestyle* or behavio?r)).ti,ab. 77524
29 (orlistat or xenical).tw,ot. 3819
30 ("Ro 18 0647" or Ro 18-0647 or Ro 180647 or Ro18647).tw,ot. 7

31 (sibutramin$ or arcalion).tw,ot. 1764
32 (Bts 54 524 or Bts 54524 or Bts54524).tw,ot. 20
33 (reductil or medaria or meridia).tw,ot. 748
34 (rimonabant or acomplia or zimulti).tw,ot. 2427
35 (Sr 141716 or Sr141716 or Sr 141716a or Sr141716a).tw,ot. 3048
36 ((eating adj2 disorder*) or bulimi* or purg*).ti,ab. 44500
37 (selfimage or self image or bodyimage or body image).mp. 32765
38 (Eating adj2 Disorder*).mp. 43893
39 or/36-38 83480
40 or/5-35 771626
41 4 and 39 and 405072
42 randomized controlled trial/ 708056
43 single blind procedure/ or double blind procedure/ 238586
44 crossover procedure/ 70276
45 random*.tw. 1786455
46 (((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin square or assign* or allocat* or volunteer*).ti,ab. 1196596
47 or/42-46 2600059
48 41 and 47 824
49 (exp animals/ or nonhuman/) not human/ 6952191
50 48 not 49 **816**

Appendix 2.3 Systematic review- Detailed table of study characteristics

Table of characteristics of included studies

Study and country	Intervention in detail	Intervention in brief	Population	Provider	Duration	Long term follow-up	Total or partial meal replacement	Eligible comparison	Age, mean years (±SD)	Participants,% female	Ethnicity, % White
Berk et al., 2018 [122]	***VLCD+ group CBT***: Starts with a diet very low in energy (very low calorie diet; VLCD) of approximately 750 kcal/day for 8 weeks. Blocks of 20 participants started with the diet concomitantly. The daily diet consisted of two diabetes-specific meal replacements plus 75 g lean meat, 150 ml skimmed milk and low-carbohydrate vegetables ad libitum. After 8 weeks the diet was changed into a low energy diet of 1100–1300 kcal/day, gradually increasing the intake during the following 12 weeks. From then on, the participants ate a diet based on national health recommendations, aiming at weight maintenance. In the end of the diet, participants started group-CBT with up to ten participants per group. The first ten weekly sessions were followed by two fortnightly sessions, two monthly sessions and two 3monthly sessions.	Very low calorie diet, re-introduction of food and then cognitive behavioural therapy	Overweight and obese (BMI >27 kg/m2) adults with type 2 diabetes and aged 18–75	Trained psychologist/psychotherapist, dietitian, diabetes nurse	18m (higher intensity up till ~6 months)	2 years	YES	X	52.3 ± 11.3	53%	50.6%

	VLCD: Starts with a diet very low in energy (very low calorie diet; VLCD) of approximately 750 kcal/day for 8 weeks. Blocks of 20 participants started with the diet concomitantly. The daily diet consisted of two diabetes-specific meal replacements plus 75 g lean meat, 150 ml skimmed milk and low-carbohydrate vegetables ad libitum. After 8 weeks the diet was changed into a low energy diet of 1100–1300 kcal/day, gradually increasing the intake during the following 12 weeks. From then on, scheduled visits every 3–6 months (sometimes on separate occasions) to the internist and diabetes nurse, plus referral to a dietitian or psychologist when indicated.	Very low calorie diet and then re-introduction of food		Dietitian, diabetes nurse ±trained psychologist/psychotherapist	~6 months	2 years	YES	X	55.2 ± 9.3	58.7%	60%
Grilo et al., 2005 [123]	***Diet + Pharmacotherapy + CBT self-help***: Treatment was administered in double-blind placebo-controlled fashion. Participants received a fixed dose of 120 mg orlistat 3 times/day with meals during the 12-week study along with basic medication management procedures. Participants were instructed to adhere to the following guidelines: 1) eat three meals and two to three snacks per day; 2) aim for modest	Moderate energy restriction food based weight loss, weight loss medication (orlistat) and cognitive behavioural therapy self-help guidance	Adults between the age 35-60, living with obesity and meeting full DSM-IC criteria for binge eating disorder	Doctors	3 months	6 months	NO	X	45.2 ± 7.4	84%	88%

	balanced calorie diet with goals of 1200 kcal/day for women and 1500 kcal/day for men; 3) limit fat to less than 30% of intake; and 4) follow United States Department of Agriculture (USDA) Food Guide Pyramid to aid in balanced food choices and portion sizes. The CBT was administered individually using a guided-self-help approach. Participants were given a copy of Overcoming Binge Eating, 25 a step-by-step self-help version of the therapist manual. The guided-self-help protocol included six brief (15–20 min) individual meetings with doctoral research-clinicians during the 12-week study. The focus was primarily on (a) maintaining and enhancing motivation; (b) correcting misunderstanding of the information; (c) addressing difficulties with relevant skill-building exercises; and (d) reinforcing the importance of self-monitoring and record keeping.										
	Diet + placebo + CBT self-help: Along with a placebo tablet 3 times/day, following guidelines: 1) eat three meals and two to three snacks per day; 2) aim for modest	Moderate energy restriction food based weight loss,		Doctors	3 months	6 months	NO	X	47 ± 7	92%	88%

	balanced calorie diet with goals of 1200 kcal/day for women and 1500 kcal/day for men; 3) limit fat to less than 30% of intake; and 4) follow United States Department of Agriculture (USDA) Food Guide Pyramid to aid in balanced food choices and portion sizes. The CBT was administered individually using a guided-self-help approach. Participants were given a copy of Overcoming Binge Eating, 25 a step-by-step selfhelp version of the therapist manual.9 The guided-selfhelp protocol included six brief (15–20 min) individual meetings with doctoral research-clinicians during the 12-week study. The clinicians focused primarily on (a) maintaining and enhancing motivation; (b) correcting misunderstanding of the information; (c) addressing difficulties with relevant skill-building exercises; and (d) reinforcing the importance of self-monitoring and record keeping.	placebo and cognitive behavioural therapy self-help guidance									
Wilfley et al., 2002 [124]	***Individualised weight loss+ Group CBT for BED***: In the first phase of the CBT phase (sessions 1-6), behavioural strategies (eg, self-monitoring) were used to help patients identify	Cognitive behavioural therapy in a group setting, with setting personalised	Adults aged 18-65 years, living with overweight/ obesity (27-48 kg/m^2)	Therapists	6 months	10 months	NO	X	45.6 ± 9.6	82.7%	93.9%

	episodes of over-restriction and under-restriction and encouraged normalising of eating patterns. During the second phase (sessions 7-14), patients learned cognitive skills to counter negative thoughts identified as predisposing binge eating. Cognitive restructuring helps patients challenge harsh stereotyped views of overweight and promotes acceptance of diverse body sizes. In the third phase (sessions 15-20), relapse prevention techniques, such as problem solving and coping with high-risk situations, are presented to help with maintaining changes. Patients are encouraged to identify reasonable goals and strategies for weight loss that will not promote binge eating.	goals for weight loss	and meeting DSM-/V research criteria for binge-eating disorder								

Calugi et al., 2016 [125]	***Inpatient weight loss + CBT***: The residential program lasted 21 days, and included the following procedures: (i) a low calorie diet (1,200 kcal/day, 50% of which from carbohydrates, 15% from proteins, and 30% from fat); (ii) 30 min per day of indoor cycling and two 45-min sessions per week of calisthenics and (iii) daily group CBT sessions. The group CBT sessions included the following strategies and procedures: (i) education on energy balance, the food pyramid, portion size, regular eating, calorie counting, shopping and food labels, physical activity (what, when, and how much); (ii) self-monitoring of food intake, energy and body weight; (iii) stimulus control strategies (in particular how to at home); (iv) problem solving; (v) cognitive restructuring of dysfunctional thoughts that hinder weight loss and weight-loss maintenance; (vi) relapse prevention; (vii) involving significant others to create an environment that facilitates adherence to lifestyle modification aimed at weight loss. The behavioural component of the treatment was based on the	Moderate energy restriction inpatient weight loss programme (based on LEARN) with cognitive behavioural therapy	Females aged 18-65, referred for inpatient obesity treatment Females aged 18-65 with binge eating disorder, referred for inpatient obesity treatment	Hospital staff	~1 month intensive and then as outpatient (in total 6 months)	X	NO	X	41.6 ± 13.4 38.8 ± 13.7	100%	Not reported

	principles of the LEARN program for weight control[262] and the cognitive component on the CBT for obesity developed by Cooper et al.[263]										
Carbone et al., 2021 [126]	***Pharmacotherapy + diet:*** Participants started with 1x tablet a day of naltrexone-bupropion available as prolonged release (containing 8 mg of naltrexone·HCl	Moderate energy restriction weight loss programme	Adults aged 18-65, meeting DSM-5 criteria for	Medical staff	4 months	X	NO	X	41 ± 13.2 44.4 ± 14	79% 53%	Not reported

	and 90 mg of bupropion·HCl) and then slowly increased to a maximum of 2 tablets twice a day after the third week. Therapy lasted for another 13 weeks, making a total of 16 weeks. Participants were allowed not to receive the maximum dose in cases of bearable side effects (e.g., nausea, constipation). Alongside the pharmacotherapy, participants were prescribed a hypo-caloric diet (reducing daily calorie intake of about 500 kcal), behavioural counselling and moderate aerobic physical activity (i.e., 20-min walk every day) during the 16 weeks.	paired with weight-loss medication (naltrexone-bupropion)	binge eating disorder diagnosis and obesity (BMI ≥30 kg/m^2) Adults aged 18-65, living with obesity (BMI ≥30 kg/m^2)								
Carels et al., 2021 [127]	***Behavioural weight loss programme + psychological intervention (self-compassion skills training)***: The BWLP was an abridged adaptation of a 12- week of the Diabetes Prevention Programme[264]. Chapters emphasized calorie and macronutrient tracking, increased exercise, self-monitoring, general tips for reducing caloric and fat intake and behaviour-focused interventions (e.g., learning cues and triggers for overeating). Participants were offered a	Moderate energy restriction weight loss programme (based on DPP), paired with self-compassion skills training	Adults aged 18 or older, BMI≥27 kg/m^2	Graduate trainees in a Clinical Psychology Doctoral programme, supervised by a licensed psychologist	3 months	X	NO	X	52 ± 12.6	76.9%	42.3%

	workbook and the focus each week was on one chapter during group sessions. Participants were encouraged to monitor their energy intake using the MyFitnessPal application, a free calorie counter (MyFitnessPal.com or a smartphone application version). Weekly groups were facilitated by graduate trainees in a Clinical Psychology Doctoral programme, supervised by a licensed psychologist. Each group had between 5 and 15 participants. The BWLP intervention was supplemented with brief self-compassion skills training. Self-compassion was framed as a supportive tool to nurture adaptive cognitive and behavioural changes throughout the weight loss program, and included the following topics: self compassionate eating, self-appreciation, evaluation of critical self-talk, increasing SC through writing, journaling, and self-care. Training consisted of psychoeducation and associated discussion regarding the application of self-compassion to support physical and psychological health.										

	Behavioural weight loss programme alone: The BWLP was an abridged adaptation of a 12-week of the Diabetes Prevention Programme[265]. Chapters emphasized calorie and macronutrient tracking, increased exercise, self-monitoring, general tips for reducing caloric and fat intake and behaviour-focused interventions (e.g., learning cues and triggers for overeating). Participants were offered a workbook and the focus each week was on one chapter during group sessions. Participants were encouraged to monitor their energy intake using the MyFitnessPal application, a free calorie counter (MyFitnessPal.com or a smartphone application version). Weekly groups were facilitated by graduate trainees in a Clinical Psychology Doctoral programme, supervised by a licensed psychologist. Each group had between 5 and 15 participants.	Moderate energy restriction weight loss programme (based on DPP)	Adults aged 18 or older, BMI≥27 kg/m^2	Graduate trainees in a Clinical Psychology Doctoral programme, supervised by a licensed psychologist	3 months	X	NO	X	52.4 ± 12.1	85.7%	64.3%

Chao et al., 2019 [128]	***Intensive Behavioural therapy only***: The programme consisted of 21 sessions of IBT, delivered by a physician, nurse practitioner, or registered dietitian. Sessions were structured, lasted 15 minutes, and were delivered as 4 weekly visits, then 10 every-other-week sessions, followed by 7 visits every 4 weeks. Participants with a weight of <113.6 kg were prescribed a diet of 1,200 to 1,499 kcal/d of conventional foods, and those with a weight of ≥113.6 kg were prescribed 1,500 to 1,800 kcal/d. Approximately 15% to 20% of kilocalories were from protein, 20% to 35% from fat, and the remainder from carbohydrates. Participants were instructed to record their food and calorie intake daily. They were encouraged to engage in low- to moderate-intensity physical activity 5 days per week, gradually building to ≥225 min/week from weeks 25 to 52. The CMS-based IBT program followed an abbreviated lifestyle counselling protocol adapted from the Diabetes Prevention Program DPP[265] for delivery in primary care settings.	Mild energy restriction weight loss programme (based on DPP)	Adults aged 21 to 70 years, BMI 30-55 kg/m^2	Physician, nurse practitioner, or registered dietitian	6 months	12 months	NO	X	49.5 ± 11	78%	54%

	Intensive Behavioural therapy + liraglutide: : The programme consisted of 21 sessions of IBT, delivered by a physician, nurse practitioner, or registered dietitian. Sessions were structured, lasted 15 minutes, and were delivered as 4 weekly visits, then 10 every-other-week sessions, followed by 7 visits every 4 weeks. Participants with a weight of <113.6 kg were prescribed a diet of 1,200 to 1,499 kcal/d of conventional foods, and those with a weight of ≥113.6 kg were prescribed 1,500 to 1,800 kcal/d. Approximately 15% to 20% of kilocalories were from protein, 20% to 35% from fat, and the remainder from carbohydrates. Participants were instructed to record their food and calorie intake daily. They were encouraged to engage in low- to moderate-intensity physical activity 5 days per week, gradually building to ≥225 min/week from weeks 25 to 52. The CMS-based IBT program followed an abbreviated lifestyle counselling protocol adapted from the Diabetes Prevention Program DPP[265] for delivery in primary care settings. Participants were also prescribed	Mild energy restriction weight loss programme (based on DPP) + medication (liraglutide)	Adults aged 21 to 70 years, BMI 30-55 kg/m^2	Physician, nurse practitioner, or registered dietitian			NO	X	45.2 ± 12.3	84%	

	liraglutide 3.0 mg/day as an once-daily, self-administered, subcutaneous injection. As recommended, the medication was initiated at 0.6 mg/d for 1 week and increased by 0.6 mg/d in weekly intervals until 3.0 mg/d was achieved.										
	Intensive Behavioural therapy with 12-week total diet replacement+ liraglutide : The programme consisted of 21 sessions of IBT, delivered by a physician, nurse practitioner, or registered dietitian. Sessions were structured, lasted 15 minutes, and were delivered as 4 weekly visits, then 10 every-other-week sessions, followed by 7 visits every 4 weeks. Participants with a weight of <113.6 kg were prescribed a diet of 1,200 to 1,499 kcal/d of conventional foods, and those with a weight of ≥113.6 kg were prescribed 1,500 to 1,800 kcal/d. Approximately 15% to 20% of kilocalories were from protein, 20% to 35% from fat, and the remainder from carbohydrates. Participants were instructed to record their food and calorie intake daily. They were encouraged to engage in low- to moderate-intensity physical	Mild energy restriction weight loss programme (based on DPP) followed by a 12-week total diet replacement regimen, paired with medication (liraglutide)	Adults aged 21 to 70 years, BMI 30-55 kg/m^2	Physician, nurse practitioner, or registered dietitian			YES	X	48 ± 11.9	76%	

	activity 5 days per week, gradually building to ≥225 min/week from weeks 25 to 52. The CMS-based IBT program followed an abbreviated lifestyle counselling protocol adapted from the Diabetes Prevention Program DPP[265] for delivery in primary care settings. Participants were prescribed liraglutide 3.0 mg/d as a once-daily, self-administered, subcutaneous injection. As recommended, the medication was initiated at 0.6 mg/d for 1 week and increased by 0.6 mg/d in weekly intervals until 3.0 mg/d was achieved. These participants received the same treatment as those in IBT-liraglutide except that, at week 4, they were prescribed a 12-week, 1,000- to 1,200-kcal/d diet that provided four servings daily of a liquid shake (Health Management Resources, Boston, Massachusetts; 160 kcal per shake) and an evening meal of a frozen food entrée (250-300 kcal), with a serving of fruit and salad.										
da Luz et al., 2017 [129]	***Subtle dieting + psychological support***: HAPIFED is a manualized program composed of five stages[129]. Stage one (sessions 2–11) mainly offers	Mild energy restriction weight loss programme with	Adults with BMI 27-40 kgm^2 and presence of recurrent	Therapists and nutritionists/dietitians	6 months	12 months	NO	X	40.55 ± 11.7	96%	75%

	psychoeducation about ED symptoms and behaviours and weight, in relation to mental and physical risks. Real-time self-monitoring is introduced and encouraged, with the additional evaluation of internal cues related to hunger and satisfaction. Stage two (session 12): the personal formulation process is revised and improved. A joint review of progress/identifying barriers to change is conducted and each participant had the opportunity to discuss/share/reflect on her/his own formulation. In other sessions, when issues emerged for the participant relevant to the formulation, the therapists explored these, linking theory to practice, with reference to the situation referred by the participant. Stage three (sessions 13–19): the focus is on behavioural change and monitoring through the practice of specific behavioural skills, e.g. activities that emphasize the identification of body's positive aspects, tasks that promote better self-care, and skills training in progressive muscular behavioural relaxation, etc. Stage four (sessions 20–27) highlights the relevance of	psychoeducation on disordered eating and	binge eating with diagnosis of BN, BED, or OSFED/UFED according to the DSM-5 criteria								

	changing unhealthy beliefs and attitudes for modification of unsuitable ED behaviours. Stage five (sessions 28–30) includes management of relapses and recheck of healthy cognitive and behavioural strategies. Features unique to HAPIFED include psychoeducation around ED and high weight, the monitoring of internal cues of hunger and satiety, dietitian-led nutritional counselling, and weight loss strategies including increased physical activity. Also, two home visits by an occupational therapist for evaluation of the domestic environment and the person's daily routines, and advice on improvements for food preparation and physical activities (in stages 1 and 3) were included.										

DalleGrave et al., 2020 [130]	***Weight loss + psychotherapy***: CBT-OB associates specific physical activity (i.e. reducing sedentary activities and gradually increasing the number of daily steps until the goal of 10,000–12,000 steps per day is reached) and dietary recommendations strategies (i.e. a meal plan based on Mediterranean diet to produce a 500- kcal energy deficit per day with cognitive behavioural procedures. Except for the first two sessions, in which the therapist describes the use of meal planning, self-monitoring in real time, and the strategies for developing an active lifestyle, sessions are dedicated to discussing how to address the weight-loss obstacles that each participant has identified in their Weight-Loss Obstacles Questionnaire—a self-report questionnaire that includes key questions investigating whether or not they are applying the treatment procedures, and whether any other behaviours or attitudes that might hinder weight loss have occurred over the previous week. By encouraging patients to change the way that they behave and analyse the	Moderate energy restriction weight loss programme (based on the Mediterranean diet), paired with cognitive behavioural therapy for obesity	Adults aged 20-65 with a BMI ≥30 kg/m^2, without severe psychiatric disorders like bulimia nervosa	3 physicians, two of whom specialise in clinical nutrition and one in nursing	18 months	N/A	NO	X	45.8 ± 11.1	76%	Not reported

	effects and implications of such behavioural modifications, CBT-OB promotes cognitive change (i.e. reduction of unrealistic weight-loss expectations, improvement in satisfaction with progress achieved during treatment, improvement in dietary restraint, reduction in disinhibition, improvement in satisfaction with the results achieved), training patients to manipulate not only their behaviour, but also their frame of mind. By being encouraged to try different ways of behaving and assessing the effects and implications thereof, patients are given an opportunity to develop a healthier approach to eating. Once new, healthier eating and physical activity habits have become the new norm, and patients have developed a persistent weight-control mind-set, they are helped to identify stimuli that are likely to "reinstall" their unhealthy weight-gain mind-set; they are taught to recognize the signs that this is occurring, and to take the appropriate action immediately (generally doing the opposite of the behaviour driven by the weight-gain mind-set). These skills										

	are designed to help patients to deal effectively and efficiently with setbacks that might otherwise develop into a full-scale relapse.										
Mensinger et al., 2016 [131]	***Weight loss programme***: Participants received the LEARN Program for Weight Management, which stands for Lifestyle, Exercise, Attitudes, Relationships, and Nutrition[262]. This evidence-based behaviour modification programme emphasizes weight loss as an ultimate goal of the program, while focusing on gaining skills to overcome weight loss barriers, and learning how to change diet and lifestyle. Participants received the 10th edition of the LEARN Program for Weight Management manual and the LEARN Weight Stabilization and Maintenance Guide along with the LEARN Program CD set. In addition to maintaining food diaries and	Mild energy restriction weight loss programme (based on LEARN) with exercise	Females aged 30-45 and BMI between 30 and 45 kg/m^2	Registered dietitian with over 15 years of experience working with bariatric populations and patients with type 2 diabetes within individual and group settings	6 months	2 years	NO	X	39.35 ± 3.9	100%	95%

	physical activity logs between the scheduled program meetings each week, participants were expected to complete exercises from the manual. Examples of the exercises included: (a) a self-assessment of eating risk factors, (b) a worksheet to prepare one with coping skills for "high risk situations" that might lead to overeating, (c) an eating habits checklist, (d) a nutrition quiz, and (e) an exercise quiz. Participants were also encouraged to maintain their lifestyle changes by utilizing the social support network developed during the program. Email and phone number lists were created and distributed to help facilitate this network. The programme emphasized the importance of healthy lifestyle choices and gradual sustainable change. However, the conventional weight management program made weight loss an explicit goal and focused on food intake levels based on external prescriptions and caloric restriction.										
DiMarco et al., 2009 [132]	***Standard guided self-help weight loss + motivational interviewing:*** The skill-building lesson plans include goal setting, environmental restructuring, logging, social	Guided self-help mild energy restriction weight loss	Adults aged 18 to 55, BMI between 27 and 40 kg/m^2	Therapists	3 months	X	NO	X	39.9 ± 8.84	82%	71.8%

	support, walking, positive attitude and self-talk, body image, cravings, stress, relapse prevention, "plateau busting," and confidence building. The widely used LEARN programme[262] encourages gradually losing weight, progressively increasing physical activity, and decreasing energy and fat intake through permanent lifestyle changes. The program emphasizes: (a) self-monitoring of eating behaviour; (b) controlling stimuli associated with eating; (c) physical activity; (d) nutrition education; (e) modifying self-defeating thoughts and negative emotions associated with dieting and body image; (f) setting realistic goals; (g) relationships; and (h) relapse prevention and weight maintenance. The nutritional guidance is consistent with federal guidelines. In this programme, these sessions incorporated motivational interviewing techniques, such as a decisional balance exercise, aimed at encouraging participants to explore ambivalence about making changes.	programme (based on LEARN), paired with motivational interviewing									
	Standard guided self-help weight loss:	Guided self-help mild		Therapists	3 months	X	NO	X			

	The skill-building lesson plans include goal setting, environmental restructuring, logging, social support, walking, positive attitude and self-talk, body image, cravings, stress, relapse prevention, "plateau busting," and confidence building. The widely used LEARN programme[262] encourages gradually losing weight, progressively increasing physical activity, and decreasing energy and fat intake through permanent lifestyle changes. The program emphasizes: (a) self-monitoring of eating behaviour; (b) controlling stimuli associated with eating; (c) physical activity; (d) nutrition education; (e) modifying self-defeating thoughts and negative emotions associated with dieting and body image; (f) setting realistic goals; (g) relationships; and (h) relapse prevention and weight maintenance. The nutritional guidance is consistent with federal guidelines.	energy restriction weight loss programme (based on LEARN)									
Grilo et al., 2021 [133]	***Pharmacotherapy + mild weight loss advice:*** Medication offered in this intervention were naltrexone and buproprion. The up-titration schedule as follows: Study day 1,	Mild energy restriction weight loss programme with weight loss	Adults aged 18-65, meeting DSM-5 criteria for binge-eating	Not specified	3 months	6 months	NO	YES-placebo control, mini	51.17 ± 8.	92%	75%

	placebo lead-in (both groups); study days 2 and 3, 150 mg of bupropion (active-treatment group) ; study days 4 and 5, 300 mg of bupropion (active-treatment group); study days 6 through 84 (end), 50 mg of naltrexone and 300 mg of bupropion (active treatment group). At the end of 12 weeks, participants followed a down-titration protocol of 7 days of 150 mg of bupropion (active-treatment group).	medication (naltrexone and buproprion)	disorder and a BMI 30-50 kg/m^2					mal advic e			
Grilo et al., 2005 [134]	***Behavioural weight loss—guided self-help (BWLgsh):*** The intervention uses the LEARN Program for Weight Management. This programme is widely used by both participants and professionals and is frequently the manual of choice in university-based clinics, and has received empirical support for its use as a self-help method. LEARN is an acronym for lifestyle, exercise, attitudes, relationships, and nutrition. LEARN focuses on making gradual and moderate lifestyle changes with goals of moderate caloric restriction and increased physical activity to produce modest gradual weight losses. Participants were provided with a copy of the self-help	Mild energy restriction weight loss programme (based on LEARN) paired with guided self-help	Adults aged 18-60, meeting DSM-4 criteria for binge-eating disorder and a BMI≥27 kg/m^2	Not specified (universit y clinic)	3 months	X	NO	YES-mini mal advic e, no man ual	46 ± 9.2	76.3%	60.5%

	book[262], which is comprised of 16 lessons covering various aspects of weight loss. The nutritional guidance is consistent with federal guidelines. The book is structured with a series of steps that address how to assess and change eating and activity behaviours. The steps are concretely described and are presented in an additive fashion yet with redundancy to facilitate mastery. The program emphasizes: (a) self-monitoring of eating behaviour; (b) controlling stimuli associated with eating; (c) physical activity; (d) nutrition education; (e) modifying self-defeating thoughts and negative emotions associated with dieting and body image; (f) setting realistic goals; (g) relationships; and (h) relapse prevention and weight maintenance.										
Dassen et al., 2018 [135]	***Weight loss plus cognitive training:*** The programme was developed as a game specifically designed to improve cognitive ability[266]. This training was developed by the faculty's engineering department in conjunction with the authors, and was based on the working memory	Mild energy restriction weight loss programme with cognitive training online	Adults aged 18-60, living with overweight, excluding participant in treatment for an eating disorder	Not specified	~1 month	7 months	NO	NO	46.3 ± 11.9	76.5%	Not reported

	(WM) training-paradigm [267,268]. Participants had to perform 25 online WM sessions (experimental condition) or sham sessions (control condition) on a tablet or computer at home. Participants also received online psychoeducation about weight loss and a healthy lifestyle, while completing the 25 sessions of WM training at home. The lifestyle intervention included four themed sessions. The first session was available at the start of the training and focused on general principles of weight loss and motivation to lose weight. Participants were advised to keep track of their daily caloric intake via an online tool. The second session addressed topics such as the 'obesogenic' environment, healthy weight loss and nutrition, and participants were encouraged to come up with their own personal diet plan. The third lifestyle session addressed several aspects of physical activity, such as the health benefits of regular physical activity and implementing physical activities in daily life. The fourth session discussed strategies for dealing with difficult moments and gave										

	tips to maintain a healthy weight after the intervention. The lifestyle intervention was composed by the first author, using general nutrition information and principles of cognitive behavioural therapy.										
	Weight loss only: The lifestyle intervention included four themed sessions. The first session was available at the start of the training and focused on general principles of weight loss and motivation to lose weight. Participants were advised to keep track of their daily caloric intake via an online tool. The second session addressed topics such as the 'obesogenic' environment, healthy weight loss and nutrition, and participants were encouraged to come up with their own personal diet plan. The third lifestyle session addressed several aspects of physical activity, such as the health benefits of regular physical activity and implementing physical activities in daily life. The fourth session discussed strategies for dealing with difficult moments and gave tips to maintain a healthy weight after the intervention. The lifestyle intervention was composed by the first author, using	Mild energy restriction weight loss programme		Not specified	~1 month	7 months	NO	NO	50.1 ± 8.6	72.5%	Not reported

	general nutrition information and principles of cognitive behavioural therapy										
Grilo et al., 2013 [136]	***Behavioural weight loss + orlistat***: Pharmacotherapy included orlistat 120 mg 3 times daily, as a fixed-dose throughout the 4 month treatment. Medication clinical management procedures for orlistat[269] were delivered in brief individual meetings by a bilingual psychiatrist at the community centre who was trained by the investigators. Participants were educated about orlistat and how it works, instructed to take the medication three times each day (with breakfast, lunch, and dinner), and were encouraged to follow the behavioural weight loss programme closely, particularly the reduced fat intake recommendations. Brief meetings with the study physician during the course of treatment were held as needed to review adherence, problem-solve issues of non-compliance, assess side effects, and if present, methods for coping with side effects. Patients were given a once-daily multivitamin containing fat-soluble vitamins and instructed to take it two hours	Moderate energy restriction weight loss programme (based on DPP) with weight loss medication (orlistat)	Adults aged 21-65, with BMI ≥30 kg/m^2, with binge eating disorder	Orlistat: bilingual psychiatrist at the community centre who was trained by the investigators. BWL: fully bilingual masters' and doctoral-level clinicians at the community centre	4 months	6 months	NO	NO	45.9 ± 9 47.8 ± 12.3	85% 85%	100%

	prior to the study medication at dinner. BWL consisted of a culturally-enhanced adaptation of the Diabetes-Prevention-Programme delivered in Spanish by fully bilingual masters' and doctoral-level clinicians at the community centre. The DPP[264] focuses on goal-setting including reasonable weight loss, healthy eating behaviours and nutritional practices, lifestyle physical activity, and problem-solving to overcome barriers to achieve these lifestyle changes. Our adaptations included the use of handouts and examples geared to the Latino/a population of Connecticut (largely Puerto Rican and mixture of South American countries), and culture-specific food props to teach healthy portion size and combinations. Following initial training in BWL and DPP methods by the investigators, the clinicians participated in the cultural adaptation process jointly with the investigators, and subsequently received weekly supervision in BWL delivery by one of the investigators. Key features of the Lifestyle Balance programme included the following elements: 1)										

	a goal-based behavioural intervention, 2) case managers or "lifestyle coaches" to deliver the intervention, 3) frequent contact and ongoing intervention throughout the trial to help participants achieve and maintain the weight and physical activity goals, 4) "toolbox" strategies to tailor the intervention to the individual participant, 5) intervention materials and strategies to address the needs of an ethnically diverse population, and 6) an extensive local and national network that provided training, feedback, and clinical support for the interventionists. The calorie goals were calculated by estimating the daily calories needed to maintain the participant's starting weight and subtracting 500–1,000 calories/day (depending on initial body weight) to achieve a 1–2 pound per week weight loss. The fat goals, given in grams of fat per day, were based on 25% of calories from fat. Four standard calorie levels were used: 1,200 kcal/day (33 g fat) for participants with an initial weight of 120–170 lbs, 1,500 kcal/day (42 g fat) for participants with a weight										

	of 175–215 lbs, 1,800 kcal/day (50 g fat) for participants with a weight of 220–245 lbs and 2,000 kcal/ day (55 g fat) for participants weighing >250 lbs.										
	Behavioural weight loss + placebo: BWL consisted of a culturally-enhanced adaptation of the Diabetes-Prevention-Programme delivered in Spanish by fully bilingual masters' and doctoral-level clinicians at the community centre. The DPP[264] focuses on goal-setting including reasonable weight loss, healthy eating behaviours and nutritional practices, lifestyle physical activity, and problem-solving to overcome barriers to achieve these lifestyle changes. Our adaptations included the use of handouts and examples geared to the Latino/a population of Connecticut (largely Puerto Rican and mixture of South American countries), and culture-specific food props to teach healthy portion size and combinations. Following initial training in BWL and DPP methods by the investigators, the clinicians participated in the cultural adaptation process jointly with the investigators, and subsequently	Moderate energy restriction weight loss programme (based on DPP) with placebo	Adults aged 21-65, with BMI ≥30 kg/m^2 without binge eating disorder	BWL: fully bilingual masters' and doctoral-level clinicians at the community centre	4 months		NO	NO	45.6 ± 7.6 46.7 ± 10.5	70% 84%	100%

	received weekly supervision in BWL delivery by one of the investigators. Key features of the Lifestyle Balance programme included the following elements: 1) a goal-based behavioural intervention, 2) case managers or "lifestyle coaches" to deliver the intervention, 3) frequent contact and ongoing intervention throughout the trial to help participants achieve and maintain the weight and physical activity goals, 4) "toolbox" strategies to tailor the intervention to the individual participant, 5) intervention materials and strategies to address the needs of an ethnically diverse population, and 6) an extensive local and national network that provided training, feedback, and clinical support for the interventionists. The calorie goals were calculated by estimating the daily calories needed to maintain the participant's starting weight and subtracting 500–1,000 calories/day (depending on initial body weight) to achieve a 1–2 pound per week weight loss. The fat goals, given in grams of fat per day, were based on 25% of calories from fat. Four										

	standard calorie levels were used: 1,200 kcal/day (33 g fat) for participants with an initial weight of 120–170 lbs, 1,500 kcal/day (42 g fat) for participants with a weight of 175–215 lbs, 1,800 kcal/day (50 g fat) for participants with a weight of 220–245 lbs and 2,000 kcal/ day (55 g fat) for participants weighing >250 lbs. Participants were also offered placebo 3 times daily, in a fixed dose throughout the 4 month treatment.										
Abiles et al., 2013 [137]	***Behavioural weight loss + cognitive behavioural therapy (CBT):*** CBT was applied in three stages in consecutive groups of 10 patients each. 1st stage (Initial psychological assessment): Tests validated for Spanish-speaking populations were used to examine the psychological profiles of patients before their group assignment for the 2nd stage, considering four variables. 2nd stage (Group therapy): Over a three-month period, CBT was applied in 12 two-hour sessions using the method of Fairburn et al.[263]. The objective of the treatment was for the patient to recover self-esteem and develop	Moderate energy restriction weight loss programme paired with cognitive behavioural therapy	Adults aged 18-59, with binge eating disorder, in the pathway for bariatric surgery Adults aged 18-59, without binge eating disorder, in the pathway for bariatric surgery	Nutritionist	3 + 12 months	X	NO	NO	42.6 ± 9.1 39.2 ± 9.1	65.3% 63.9%	Not reported

	appropriate eating behaviours for weight loss and long-term weight maintenance. It was necessary for patients to lose at least 10% of their initial weight to complete the CBT and be accepted for BS. 3rd stage (Individual monitoring and treatment): After the group therapy stage, patients again underwent psychopathology assessment to detect behaviours needing reinforcement or symptoms requiring individual treatment. Next, patients were followed up in weekly 60-min sessions for 12-months, and their suitability for BS was then evaluated in a final report. Throughout this 12 month period, the calorie intake of the patients was restricted by following a balanced diet of 1,500 kcal in accordance with guidelines provided by a nutritionist.										
Grilo et al., 2020 [138]	***BWL + pharmacotherapy***: In this stepped care protocol, patients began behavioural weight loss (BWL) which lasted for 1 month. Treatment responders continued BWL, whereas non-responders switched to cognitive behavioural therapy, and all were randomized (double-blind) to	Mild energy restriction weight loss programme (based on LEARN) with weight loss medication (sibutramine	Adults aged 18-65, BMI 30-50 kg/m^2 and meeting DSM-4 for binge eating disorder	Master's-level clinicians delivered BWL, and a faculty-level psychiatrist	6 months	X	NO	NO	48 ± 9.6 50 ± 9.2	68% 82.1 %	78.9% 77%

	weight-loss medication or placebo (5 months). BWL was based on the LEARN Program for Weight Management[262]. The widely used LEARN program encourages gradually losing weight, progressively increasing physical activity, and decreasing energy and fat intake through permanent lifestyle changes. The program emphasizes: (a) self-monitoring of eating behaviour; (b) controlling stimuli associated with eating; (c) physical activity; (d) nutrition education; (e) modifying self-defeating thoughts and negative emotions associated with dieting and body image; (f) setting realistic goals; (g) relationships; and (h) relapse prevention and weight maintenance. BWL was delivered in individual sessions ranging from 50 to 60 minutes following the manual and keyed to specific patient readings in their copy of the self-care manual and to weekly behavioural goals, moderate caloric reductions with improved nutrition quality (1,200- 1,500 kcal/day, less than 30% fat), and moderate increases in physical activity (30 minutes of physical activity five times weekly).	first but then changed to orlistat as sibutramine discontinued)		delivered pharmaco therapy with minimal clinical managem ent							

	Behavioural strategies include goal setting, recording food intake and physical activity, and problem solving to cope with barriers to attaining goals. Sibutramine, a serotonin/norepinephrine reuptake inhibitor, was given using fixed doses of 15 mg/d (38) during the last 5 months of Stepped Care. When sibutramine was withdrawn from the market (October 2010), the study was continued as conceptually designed using the FDA-approved weight-loss medication orlistat in a dose of 120 mg, three times daily.										
	BWL + placebo: In this stepped care protocol, patients began behavioural weight loss (BWL) which lasted for 1 month. Treatment responders continued BWL, whereas non-responders switched to cognitive behavioural therapy, and all were randomized (double-blind) to weight-loss medication or placebo (5 months). BWL was based on the LEARN Program for Weight Management[262]. The widely used LEARN program encourages gradually losing weight, progressively increasing physical	Mild energy restriction weight loss programme (based on LEARN) with placebo		Master's-level clinicians delivered BWL, and a faculty-level psychiatrist delivered pharmacotherapy with minimal clinical	6 months	X	NO	NO	45.9 ± 9.0	85%	0%

	activity, and decreasing energy and fat intake through permanent lifestyle changes. The program emphasizes: (a) self-monitoring of eating behaviour; (b) controlling stimuli associated with eating; (c) physical activity; (d) nutrition education; (e) modifying self-defeating thoughts and negative emotions associated with dieting and body image; (f) setting realistic goals; (g) relationships; and (h) relapse prevention and weight maintenance. BWL was delivered in individual sessions ranging from 50 to 60 minutes following the manual and keyed to specific patient readings in their copy of the self-care manual and to weekly behavioural goals, moderate caloric reductions with improved nutrition quality (1,200- 1,500 kcal/day, less than 30% fat), and moderate increases in physical activity (30 minutes of physical activity five times weekly). Behavioural strategies include goal setting, recording food intake and physical activity, and problem solving to cope with barriers to attaining goals. Sibutramine, a serotonin/norepinephrine reuptake inhibitor, was given using			managem ent							

	fixed doses of 15 mg/d (38) during the last 5 months of Stepped Care. When sibutramine was withdrawn from the market (October 2010), the study was continued as conceptually designed using the FDA-approved weight-loss medication orlistat in a dose of 120 mg, three times daily. Placebo was delivered in a double-blind (matched identical capsules) manner with minimal clinical management										
	BWL alone: BWL was based on the LEARN Program for Weight Management[262]. The widely used LEARN program encourages gradually losing weight, progressively increasing physical activity, and decreasing energy and fat intake through permanent lifestyle changes. The program emphasizes: (a) self-monitoring of eating behaviour; (b) controlling stimuli associated with eating; (c) physical activity; (d) nutrition education; (e) modifying self-defeating thoughts and negative emotions associated with dieting and body image; (f) setting realistic goals; (g) relationships; and (h) relapse prevention and weight	Mild energy restriction weight loss programme (based on LEARN)		Master's-level clinicians delivered BWL	6 months	X	NO	NO	45.6 ± 7.6	70%	

	maintenance. BWL was delivered in individual sessions ranging from 50 to 60 minutes following the manual and keyed to specific patient readings in their copy of the self-care manual and to weekly behavioural goals, moderate caloric reductions with improved nutrition quality (1,200- 1,500 kcal/day, less than 30% fat), and moderate increases in physical activity (30 minutes of physical activity five times weekly). Behavioural strategies include goal setting, recording food intake and physical activity, and problem solving to cope with barriers to attaining goals.										
Loader et al., 2013 [139]	***Behavioural weight loss + guided bibliotherapy self help:*** Behavioural weight loss was treatment as usual (TAU) consisted of the current support available from the weight management clinic. This support was initially a one-to-one appointment with a doctor and an invitation to attend a psycho-education group. This group provided information on factors affecting weight such as nutrition and activity levels. The initial group session lasted approximately an hour and a half	Mild energy restriction weight loss with self-help guided compassion learning	Adults aged 18-65, BMI≥30 kg/m^2, at a specialist NHS weight management clinic	BWL was delivered by a Dr and a dietitian. Therapists were Trainee Clinical Psychologists who had undergone training. Supervisi	6 months	X	NO	NO	46.4 ± 9.7	66%	88.9%

	and could include potentially 12 new patients. TAU was for an indeterminate period depending on the individual's presentation. During their involvement with the clinic the average patient would attend regular assessment reviews with a doctor and a dietician and be invited to attend assessment group sessions. Support and advice was offered regarding diet, physical activity and lifestyle changes to encourage weight-loss. The BWL was supplemented with guided self-help (GSH) bibliotherapy. The bibliotherapy manual was "Compassionate mind approach to beating overeating"[270]. Participants were asked to work through this manual at approximately one chapter every two weeks. They also received prearranged telephone support calls every two weeks facilitated by a therapist. Each telephone call was intended to offer support which focused on a relevant chapter of the manual. The calls were scheduled to last approximately 15 minutes and follow a protocol which was used as a prompt. If participants were unable to attend their telephone			on was available from a Consultant Clinical Psychologist.							

	appointment then an alternative was arranged. The intervention lasted for six months and a maximum of 12 support telephone calls were offered.										
	Behavioural weight loss alone: Behavioural weight loss was treatment as usual (TAU) consisted of the current support available from the weight management clinic. This support was initially a one-to-one appointment with a doctor and an invitation to attend a psycho-education group. This group provided information on factors affecting weight such as nutrition and activity levels. The initial group session lasted approximately an hour and a half and could include potentially 12 new patients. TAU was for an indeterminate period depending on the individual's presentation. During their involvement with the clinic the average patient would attend regular assessment reviews with a doctor and a dietician and be invited to attend assessment group sessions. Support and advice was offered regarding diet, physical activity and lifestyle changes to encourage weight-loss.	Mild energy restriction weight loss		BWL was delivered by a Dr and a dietitian.	6 months	X	NO	NO	44.3 ± 9.5	72%	61.1%

Nauta et al., 2000 [140]	***Behavioural weight loss:*** The aim of the treatment was to learn a healthy eating pattern by having three meals each day and three planned snacks, decreasing fat intake, eating between 1,500 to 1,800 kcal a day, increasing exercise habits, and recognizing and anticipating high-risk situations. In the first session, the therapists explained the rationale of behavioural therapy: To regain control over eating, it is important to learn a healthy eating pattern, without excessive, restrictive dieting. Participants were told that treatment needed first to eliminate binge eating and overeating patterns by establishing regular, healthy eating patterns and that weight control needed to be a secondary concern. Participants were instructed to self-monitor their food intake and eating patterns, binge episodes, or episodes of overeating and the circumstances under which they occurred (i.e., time or mood). Examination of the self-monitoring formed an important focus of therapy. In the first half of the session, homework assignments were discussed, and in the second	Mild energy restriction weight loss programme with stimulus control techniques	Adults aged 18-50, with BMI≥ 27 kg/m^2 and without binge eating Adults aged 18-50, with BMI≥ 27 kg/m^2 and meeting DSM-4 diagnostic criteria for binge eating	Therapists experienced in the behavioural and cognitive treatment of eating disorders and/ or obesity	4 months	10 months	NO	NO	38.3 ± 7.1	100%	Not reported

	half, nutritional information was given. Furthermore, participants were advised to make gradual changes in eating habits and exercise level. The basic behavioural strategies were self-monitoring, goal-setting, and stimulus control techniques. Three forms of stimulus control techniques were used. First, participants learned stimulus control techniques whereby stimuli that resulted in eating were avoided (e.g., not going to a shop when hungry). Second, they learned techniques to anticipate high-risk situations and to outline strategies to prevent eating, such as walking or taking a shower. Third, participants learned self-reinforcement techniques, such as buying a magazine, and were positively reinforced by the therapist if they were not overeating. No attention was paid to dysfunctional cognitions.										

Grilo et al., 2011 [141]	***Behavioural weight loss:*** Behavioural weight loss was administered in 16 group 60-minute sessions over a 24-week period following the manualized LEARN Program for Weight Management[262]. This specific BWL is used widely in obesity studies[271] and has been previously used in treatment trials with BED[272]. LEARN is an acronym for lifestyle, exercise, attitudes, relationships, and nutrition. LEARN focuses on making gradual lifestyle changes with goals of moderate caloric restriction and increased physical activity to produce gradual weight losses. The program emphasizes: (a) self-monitoring of eating behaviour; (b) controlling stimuli associated with eating; (c) physical activity; (d) nutrition education; (e) modifying self-defeating thoughts and negative emotions associated with dieting and body image; (f) setting realistic goals; (g) relationships; and (h) relapse prevention and weight maintenance. BWL was delivered in individual sessions ranging from 50 to 60 minutes following the manual and keyed to specific patient readings in their copy of the self-	Mild energy restriction weight loss programme (based on LEARN)	Aged 18-60 with BMI 30-65 kg/m^2, and meeting criteria for binge eating	Therapists (doctoral-level psychologists)	6 months	12 months	NO	NO	44.6 ± 8.5	62.2%	80%

	care manual and to weekly behavioural goals, moderate caloric reductions with improved nutrition quality (1,200- 1,500 kcal/day, less than 30% fat), and moderate increases in physical activity (30 minutes of physical activity five times weekly). Behavioural strategies include goal setting, recording food intake and physical activity, and problem solving to cope with barriers to attaining goals.										
	Sequential Cognitive Behavioural Therapy followed by Behavioural Weight Loss (CBT+BWL): This treatment condition involved a sequential approach in which CBT was delivered first (16 sessions over 16 weeks) followed by BWL (16 sessions over 24 weeks). The CBT and BWL interventions were delivered in group by the same therapists using the same BWL protocol as above.	Mild energy restriction weight loss programme (based on LEARN), paired with group cognitive behavioural therapy		Therapists (doctoral-level psychologists)	10 months	12 months	NO	NO	44.5 ± 9.2	80%	74.3%
Masheb et al., 2011 [142]	***Cognitive behavioural therapy (CBT) + low energy-density diet***: In the programme, each hour-long session included 40 min devoted to CBT and 20 min devoted to dietary counselling. Between weeks 1-16, one-hour weekly individual sessions were offered, whereas for	Mild energy restriction weight loss programme focussing on energy density, paired with cognitive	Adults aged 21-60, BMI≥30 kg/m^2, and meeting DSM-4 criteria for	Doctoral-level research clinicians in psychology	6 months	X	NO	NO	47.9 ± 7.9	80%	72%

	weeks 17-26, sessions were offered every other week. Sessions included 40 min devoted to CBT and 20 min devoted to energy density. Participants completed daily food diaries that were checked weekly by clinicians. In addition, participants were instructed in how to self-monitor episodes of binge eating and overeating in these diaries. Additionally, participants in this condition received weekly dietary counselling for lowering energy density. In the first phase of this treatment, patients were informed about the objective and science of energy density shown a food preparation demonstration for a breakfast differing in energy density; shown photographs of meals differing in energy density; and taught how to calculate energy density using nutrition facts labels, the energy-density formula, and an energy-density value food chart. In the second phase of this treatment, goals were set to increase the patient's consumption of low-energy-density foods which could be eaten in satisfying portions, and to exercise portion control over medium to high	behavioural therapy	binge eating disorder								

	energy-density foods. Weekly topics adapted from the manualized protocol by Ello-Martin et al.[273] were: water and energy density; reducing fat and energy density; volume and satiety; portion and serving sizes; carbohydrates and energy density; protein and energy density; calcium and energy density; beverages, alcohol and desserts; meal planning and grocery shopping; dining out and energy density; modifying recipes; overcoming obstacles to fruits and vegetables; cravings and variety; low-energy-density snacks and comfort foods; weight maintenance; and, holidays and celebrations										
	CBT plus general nutrition counselling not related to lowering energy density or weight loss: CBT- ED (21 hourly individual sessions over a six-month treatment period, weekly for weeks 1e16 and every other week for weeks 17e26, with 40 min devoted to CBT and 20 min devoted to nutrition). Participants in this condition completed food diaries and self-monitoring, and	Mild energy restriction weight loss advice with cognitive behavioural therapy	Adults aged 21-60, BMI≥30 kg/m^2, and meeting DSM-4 criteria for binge eating disorder	Doctoral-level research clinicians in psychology	6 months	X	NO	NO	43.7 ± 6.7	72%	88%

	received the same exact CBT described in Treatment 1 above. Additionally, participants in this condition received weekly dietary counselling for health as opposed to reducing energy density or weight loss. A manual was specifically designed for this study so that the CBT þ GN would serve as an active comparator to the CBT þ ED treatment.1 In the first phase of the dietary component of treatment patients were: informed about the objective of the general nutrition treatment and the science and definition of nutrients; taught the definition of calories; and informed about nutrition facts labels. In the second phase, each weekly topic was designed specifically as a control for the type and amount of dietary information provided in the energy-density condition and included the following: MyPyramid.gov and your health; dietary fat and your health; fruits, vegetables and your health; portions, serving sizes and your health; carbohydrates and your health; protein and your health; calcium and your health; water and your health; meal planning, grocery shopping and your health; dining										

	out and your health; added sugars and your health; herbs, spices and your health; consumer information and your health; sodium and your health; snacks, comfort foods and your health; vitamins, antioxidants and your health; and, tips for holidays and celebrations. Clinicians reviewed and discussed the weekly topic with patients, but no problem-solving or goal-setting was conducted in these sessions										
Munsch et al., 2007 [143]	***Behavioural weight loss***: 6 group sessions lead by therapists. The active treatment phase consisted of 16 weekly 90 min group sessions. BWLT was based on the manual "Weight Loss with Xenical". This standardized treatment was developed to foster weight management and aims at instructing patients to normalize fat intake and to achieve balanced nutrition, including lifestyle modification and a hypocaloric diet (30% of energy from fat).	Mild energy restriction weight loss programme	Adults aged 18-70, BMI 27-40 kg/m^2, meeting full DSM-IV criteria for binge eating disorder	Therapists (fully qualified psychotherapists + MSc students)	4 months	X	NO	NO	47.8 ± 11.8	86.1%	Not reported

Pataky et al., 2018 [144]	***Multidisciplinary weight loss programme:*** The Service of Therapeutic Education for Chronic Diseases is a WHO collaborating and reference centre for chronic disease management, particularly engaged in therapeutic patient education in the field of obesity and diabetes. The evaluated lifestyle intervention for weight loss is a multidisciplinary and structured patient educational program for obese patients over 12 months, with a minimum of 9 group sessions and 10 individual outpatient appointments during the program duration. Each group session, of whole day duration (from 9 a.m. to 5 p.m.) consists of several workshops having a specific structure, depending on the topic (e.g., diet, eating behaviour, physical activity). At the beginning of the program, patients are required to participate in a predefined curriculum including on medical issues, balanced diet, cognitive-behavioural therapy, physical activity, and art therapy over 4 consecutive days. During these 4 days, every patient has individual appointments with different healthcare providers	Mild energy restriction weight loss outpatient programme	Adults living with overweight/ obesity presenting for treatment	Multidisciplinary team including a dietitian	12 months	X	NO	NO	46 ± 8 47 ± 11 46 ± 9	80% 87.2% 84.6%	Not reported

	(HCP) and specialists (e.g., physician, nurse, dietician, and psychologist) for medical, nutritional and psychological assessment on an interdisciplinary basis. Moreover, group sessions take place and are managed by the HCP according to the workshop's topic. This 4-day (full time) educational program is followed by a coaching that takes place over the following 12 months. During this period, every patient participates in a minimum of 4 ambulatory, motivational and educational group sessions (every 2–3 months), each with different topic (i.e., diet, cognitive-behavioural therapy, physical activity, and body image) taking 1 day each. A personal coach (i.e., an HCP specialized in both obesity management and patient education) is attributed to every patient. The patient has a follow-up on regular monthly basis with this HCP and during the 12-month follow-up period. His/her body weight is measured monthly during each 60-min individual appointment. During these face-to-face meetings, different aspects of healthy nutrition and physical										

	activity are discussed with the patient, as well as the difficulties related to psychological and environmental issues (e.g., family, work, social live). The face-to-face meetings are individually tailored and are based on motivational interviewing, and any diet or physical activity prescription is proposed to the patient. At the end of the 12-month period, patients are required to participate in the last workshop day centred on results after 12 months. In addition to biological evaluation (e.g., fasting glucose, HbA1c, lipids, liver parameters, and blood pressure), group sessions and individual appointments take place during the day in order to assess the psychosocial well-being and quality of life for every participant.										
Preuss et al. 2017 [145]	***Weight loss programme***: Treatment focuses on therapeutic goals recommended for both patients with BED and patients with obesity and other pathological eating behaviour, by evidence-based clinical guidelines (NICE, 2014 for obesity and NICE, 2004/2017 for atypical EDs including BED). Ten modules	Mild energy restriction weight loss programme	Adults with BMI 25-40.9 kg/m^2	Clinical psychologists in advanced training for the licensure of psychological	~3 months	6 months	NO	NO	38.1 ± 10.7 38.1 ± 11.2 38.1 ± 10.1	94.2% 95.1% 92.9%	Not reported

	concerning the management of daily diet, movement und stress were constructed, based on previously evaluated CBT manuals for the treatment of obesity and BED[263,274]. Typical interventions were application of daily eating protocols and goal attainment by formulating weekly goals concerning eating and activity behaviours, promoting change in dietary habits, e.g., increasing intake of complex carbohydrates and high-fibre products, increasing daily physical activity, learning mindful eating, applying self-instruction and problem solving skills to resolve emotional eating and incorporating relaxation exercises into daily life (e.g. progressive muscular relaxation and imagery techniques).			psychoth erapy							
Ramirez et al., 2001 [146]	***Weight loss***: This intervention consisted of 16 sessions, one hour per week, led by a registered dietitian. The curriculum for the weight-control intervention as the LEARN Program for Weight Control[262], a 16-week nutrition and behavioural self-management program that L incorporates a weekly plan to promote eating and	Mild energy restriction (based on LEARN)	Adults with BMI greater or equal to 27.3 for women and 27.8 for men	Registere d dietitian	4 weeks	X	NO	NO	44 ± 9.7	77.3%	Not reported

	exercise change. (The edition of the LEARN program we used did not include any intervention for body image, whereas subsequent editions contain a brief section on this aspect.)										
Rock et al., 2010 [147]	***Centre-based weight loss intervention:*** Participants assigned to the centre based study groups received all program materials, including free-of-charge pre-packaged prepared foods as needed to achieve a meal plan. Interactions between corporate trained and supervised staff and the participants consisted of brief weekly one-to-one contacts with an in-person or telephone counsellor, with follow-up phone and e-mail contacts and Web site or message board availability. Counsellors were instructed to provide the program as designed for a regular paying client, although they were not blinded to the identity of study participants. Free of-charge counselling sessions were offered to participants for the entire 2-year period. The diet component of the program consisted of a	Moderate energy restriction weight loss programme delivered in person	Females aged 18 or older, with a BMI 25-40 kg/m^2, without a diagnosis of an eating disorder	Corporate trained and supervised staff	~ 6 months intensive, 2 years overall	12 months	NO	YES-publically available materials	44 ± 10	100%	67.7%

	nutritionally adequate, low-fat (20%-30% of energy), reduced energy diet (typically 1200-2000 kcal/d) that included pre-packaged prepared food items with increased amounts of vegetables and fruits to reduce the energy density of the diet. The approach was tailored so that participants could choose regular foods when preferred. Participants were encouraged during the initial period to follow a menu plan with pre-packaged foods, which would provide 42% to 68% of energy for those who choose not to deviate from the plan. Regular foods, such as vegetables, fruit, cereal or grain products, low-fat dairy products, lean meat or the equivalent, and unsaturated fat sources were recommended to achieve the total prescribed energy intake. Over time, participants were transitioned to a meal plan based mainly on food not provided by the commercial program, although participants could choose to include 1 pre-packaged meal per day during weight loss maintenance. Prepared foods and counsellors were provided by Jenny Craig Inc (Carlsbad,										

	California). Increased physical activity was another program component; the goal was 30 minutes of physical activity on 5 or more days per week. Program material and counselling addressed attitudes about weight, food, and physical activity and included recipes and guidance for eating in restaurants, CDs and DVDs to increase physical activity, and online tools and support										
	Telephone-based weight loss intervention: Participants assigned to the telephone based study groups received all program materials, including free-of-charge pre-packaged prepared foods as needed to achieve a meal plan. Interactions between corporate trained and supervised staff and the participants consisted of brief weekly one-to-one contacts with an in-person or telephone counsellor, with follow-up phone and e mail contacts and Web site or message board availability. Counsellors were instructed to provide the program as designed for a regular paying client, although they were not blinded to the identity of study participants. Free	Moderate energy restriction weight loss programme delivered over the phone		Corporate trained and supervised staff	~ 6 months intensive, 2 years overall	12 months	NO	YES-publically available materials	44 ± 10	100%	79.3%

	of-charge counselling sessions were offered to participants for the entire 2-year period. The diet component of the program consisted of a nutritionally adequate, low-fat (20%-30% of energy), reduced energy diet (typically 1200-2000 kcal/d) that included pre-packaged prepared food items with increased amounts of vegetables and fruits to reduce the energy density of the diet. The approach was tailored so that participants could choose regular foods when preferred. Participants were encouraged during the initial period to follow a menu plan with pre-packaged foods, which would provide 42% to 68% of energy for those who choose not to deviate from the plan. Regular foods, such as vegetables, fruit, cereal or grain products, low-fat dairy products, lean meat or the equivalent, and unsaturated fat sources were recommended to achieve the total prescribed energy intake. Over time, participants were transitioned to a meal plan based mainly on food not provided by the commercial program, although participants could choose to include 1 pre-packaged meal per										

	day during weight loss maintenance. Prepared foods and counsellors were provided by JennyCraig Inc (Carlsbad, California). Increased physical activity was another program component; the goal was 30 minutes of physical activity on 5 or more days per week. Program material and counselling addressed attitudes about weight, food, and physical activity and included recipes and guidance for eating in restaurants, CDs and DVDs to increase physical activity, and online tools and support.										
Barnes et al., 2017 [148]	***Weight loss + motivational interviewing programme:*** Intervention) included five manualized sessions over 12 weeks, with guidelines to help medical assistants flexibly apply MI strategies to motivate patients for behaviour changes that support weight loss. The guidelines allowed focus on BED as needed. The first appointment included an initial 60-minute in-person individual session. Following this first appointment, patients received up to four additional 20-minute MI sessions. At their first session,	Mild energy restriction weight loss programme (based on LEARN) paired with motivational interviewing	Adults with BMI 25-55 kg/m^2	Medical assistants	3 months	6 months	NO	YES-no intervention offered, usual care in community if they want	47.1 ± 10	80%	63%

	participants also received a Lifestyle, Exercise, Attitudes, Relationships, and Nutrition (LEARN) manual[262] and orientation to a free website for tracking food intake, setting weight and intake goals, and physical activity (Livestrong.com).										
	Nutrition psychoeducation programme: The nutrition psychoeducation and internet condition was designed as a five-session psychoeducation only, attention-control. The sessions provided basic nutritional information (e.g., recommended fruit/vegetable intake) based on the recommendations of the American Heart Association and United States Department of Agriculture and allowed patients to ask questions to better understand the material. Participants received the same manual, and opportunity to sign up and use Livstrong.com to set weight loss/calorie goals as above. However, any further discussion about motivation, food tracking, goal setting, or personalized feedback was proscribed.	Mild energy restriction weight loss nutrition psychoeducation programme (based on the American Heart Association and the US department of Agriculture)		Medical assistants	3 months	6 months	NO	YES- no intervention offered, usual care in community if they want	49 ± 11.6	69%	69%

Barnes et al., 2018 [149]	***Motivational Interviewing and Nutrition Psychoeducation:*** This was designed as a five session, manualized, 3-month intervention. MINP included guidelines to help medical assistants flexibly apply MI with strategies to motivate participants for weight-related behaviour change and allowed focus on BED as needed. The first session was an initial 60-min in person individual appointment, which focused on enhancing motivation for weight loss and treatment adherence and ending with participants setting self-identified specific weight-related goals. Clinicians interacted with their participants in a non-judgmental and collaborative fashion, conveying respect, acceptance, and compassion toward them and a stance toward evoking the participants' motives for change, consistent with a MI style of interaction. Use of MI-inconsistent strategies (e.g., confrontation) was proscribed. At the participants' discretion, the session also included basic nutrition psychoeducation (e.g., recommended fruit/vegetable intake, healthy portion and serving	Mild energy restriction weight loss programme (based on LEARN) paired with motivational interviewing and nutritional psychoeducation	Adults with BMI 25-55 kg/m^2	Medical assistants	3 months	6 months	NO	NO	48.4 ± 10.6	87.1%	41.9%

	sizes) based on the recommendations of the American Heart Association and United States Department of Agriculture. In addition, they received training in the use of supplemental materials: a free weight loss website (Livestrong.com) and a LEARN manual[262], a readily available, well-researched weight loss manual. Clinicians taught participants to login to Livstrong.com, enter pertinent information (height, weight, age, activity level) and weekly weight loss and physical activity goals. Livestrong.com then provided participants with daily calorie guidelines for attaining their goals. Participants were shown how to track food, weight, and exercise, and to monitor other nutrition related information (e.g., carbohydrate intake), and if participants desired, they received personalized feedback on food journals at subsequent sessions. Following this first appointment, participants received up to four additional 20-min MINP sessions (in-person at weeks 6, 12, by phone at weeks 3, 9). If participants were interested, each										

	session started with a discussion of the participants' specific and measurable behavioural weight-loss goals (e.g., walk 30 min 3 times a week, track food intake on Livestrong.com 4 days a week) from the previous session and ended with setting new goals, including problem-solving as necessary for when goals were not reached. Clinicians used MI strategies (e.g., reflections, affirmations, change planning) in these sessions to enhance participant motivation to meet weight-related goals (e.g., decreasing calories, increasing fruit/vegetable intake, increasing physical activity) and provided nutrition psychoeducatio***n.***										
Moss et al., 2017 [116]	***Behavioural weight-loss programme:*** TrymGym was established in 1973 at a large medical doctoral university in Calgary and over 10,000 participants have completed the program. This BWLP emphasizes gradual, sustainable weight loss and lifestyle changes, and is delivered by a team of health care practitioners including dietitians, kinesiologists, and fitness instructors via both	Mild energy restriction weight loss programme with exercise	Adults with BMI ≥25 kg/m^2	Researcher/therapist	3 months	9 months	NO	NO	45.6 ± 9.8	75.36%	95.8%

	classroom sessions and exercise sessions. Specifically, the program consists of three core components: (1) Nutrition: individualized guidelines for healthy eating, based on the Canada Food Guide[275], were developed for each participant, (2) Physical activity: group exercise classes focused on fat loss, strength training, and development of endurance and flexibility, and (3) Behaviour change: behavioural strategies including self-monitoring, goal-setting, and formulating action plans to achieve goals were taught in classroom sessions. The semi-structured MI protocol was a 45-min intervention developed by the first author based on general MI principles and guidelines[276], MI strategies specific to health care practice[277], and MI principles for and (8) eliciting ideas for possible changes participant could make to work towards weight loss. The protocol for both MI sessions consisted of similar components for obesity treatment[278]. The MI protocol included the following components: (1) eliciting concerns about weight, (2) exploring ambivalence, (3) assessing										

	importance and confidence for change, (4) writing a decisional balance, (5) bolstering self-efficacy, (6) looking towards the future.										
	Weight loss attention control: The attention control interview was a semi-structured interview addressing health history, weight history, diet history, and dietary and physical activity habits. Most questions were drawn from the TrymGym intake application. It was designed to be structurally equivalent to the MI session in length of session, timing of sessions, and treatment modality. The goal was to provide a pseudo-intervention that controlled for factors common to attending treatment (e.g., attending treatment sessions, having personal contact with a therapist, discussing weight-related issues).	Mild energy restriction weight loss		Researcher/therapist	3 months	9 months	NO	NO	44 ± 11.9	84%	Not reported

Werrij et al., 2008 [150]	***Cognitive dietetic group treatment:*** The treatment consisted of 10 weekly sessions of 2 h each. Both were provided in groups with a maximum of 12 participants. Each treatment session was divided into two parts. The first part (the first hour) was always the dietetic intervention, carried out by dieticians. This dietetic treatment part was exactly the same for both treatment conditions. The main aims of the dietetic intervention were to change unhealthy dietary patterns into more healthy ones and to improve self-control. To achieve this, nutritional education was provided, food diaries were kept, and cooking classes were given to learn healthy cooking. Dietary patterns were changed by a stepwise program, aimed at eating three meals a day, eating at a regular place, and mindful eating; slow, conscious, and without distraction. Participants were trained in changing bad eating habits into more healthy habits; they learned when to stop eating, how to refuse food, how to find social support, how to deal with parties and super market shopping,	Mild energy restriction weight loss programme with cognitive therapy	Adults aged 18-65 and BMI≥27 kg/m^2	Dietitians and fully qualified CBT therapists	2.5 months	12 months	NO	NO	44 ± 11.9	84%	Not reported

	and so on. They further received guidelines for a healthy diet but this was not a prescribed diet. Interventions in the second part (the second hour) differed between the experimental and the control treatment; in the experimental CDT condition cognitive therapy (CT) was added to the dietetic treatment, whereas in the control EDT condition physical exercise was added to the dietetic intervention. The cognitive therapy was performed by fully qualified cognitive behaviour therapists. Aims of the CT were to identify, challenge, and change dysfunctional cognitions concerning eating, control, weight, and shape, as well as related schemas (e.g., self-esteem schemas or interpersonal schemas). Automatic thoughts and beliefs were identified and challenged, and behavioural experiments were set up. Participants were provided with workbooks entitled Dik Tevreden (Pleasantly Plump) containing background information about the cognitive intervention and homework assignments, including thought diaries. An example of a frequently reported										

	dysfunctional thought related to control overeating was "whenever I start eating nuts [chocolates, candies, etc.], I have to finish the whole bowl". An example of a dysfunctional thought related to weight was "when I am this fat, I will never find nice clothes". The CBT therapists were intensely trained into the present CT protocol by the authors who are fully qualified CBT therapists and experienced in the cognitive treatment of eating disorders and obesity. There were weekly supervision sessions.										
	Exercise + dietetic treatment (EDT): The treatment consisted of 10 weekly sessions of 2 h each. Both were provided in groups with a maximum of 12 participants. Each treatment session was divided into two parts. The first part (the first hour) was always the dietetic intervention, carried out by dieticians. This dietetic treatment part was exactly the same for both treatment conditions. The main aims of the dietetic intervention were to change unhealthy dietary patterns into more healthy ones and to improve self-control. To	Mild energy restriction weight loss programme and exercise		Dietitians and fully qualified physiotherapists	2.5 months	12 months	NO	NO	45 ± 12.2	78%	Not reported

	achieve this, nutritional education was provided, food diaries were kept, and cooking classes were given to learn healthy cooking. Dietary patterns were changed by a stepwise program, aimed at eating three meals a day, eating at a regular place, and mindful eating; slow, conscious, and without distraction. Participants were trained in changing bad eating habits into more healthy habits; they learned when to stop eating, how to refuse food, how to find social support, how to deal with parties and super market shopping, and so on. They further received guidelines for a healthy diet but this was not a prescribed diet. Interventions in the second part (the second hour) differed between the experimental and the control treatment; in the experimental CDT condition cognitive therapy (CT) was added to the dietetic treatment, whereas in the control EDT condition physical exercise was added to the dietetic intervention. The cognitive therapy was performed by fully qualified cognitive behaviour therapists and fully qualified physiotherapists led the physical										

	exercise. Participants in the control condition engaged in a 1-h low intensity exercise program (gym) supervised by a qualified physiotherapist. The combination of dietetic treatment (1 h) and physical exercise (1 h) in groups is, in this Dutch field setting, the standard treatment for obesity.										
Wilson et al., 2010 [151]	***Behavioural weight loss:*** The National Institutes of Diabetes and Digestive and Kidney Diseases' Diabetes Prevention Program's manual[264] was adapted for this study. The program includes both moderate caloric restriction and exercise. The treatment initially focused on dietary change toward a weight loss goal of 7% of one's starting weight. Participants were first asked to reduce fat intake to 25% of calories from fat. If satisfactory progress in terms of weight loss was not being made a calorie goal was set based on initial weight. Self-monitoring of exercise, fat intake, and (if necessary) caloric intake is an essential aspect of the programme. The exercise goal was 2.5hours of moderate exercise each week. The core curriculum consists of 16 individual weekly sessions each lasting 50 minutes	Moderate energy restriction weight loss programme (based on DPP)	Adults with BMI 27-45 kg/m^2 and meeting DSM-4 for binge eating disorder	Master's-level therapists in clinical psychology or nutrition	6 months	12 months	NO	NO	46.2 ± 10.9	89%	88%

	and followed by 4 sessions at 2-week intervals aimed at continuing weight loss and enhancing maintenance of such losses based on the National Institutes of Diabetes and Digestive and Kidney Diseases manual for contacts after the initial core 16 sessions. The treatment was delivered by master's-level therapists in clinical psychology or nutrition, 2 at Rutgers University and 3 at Washington University. Bonnie Gillis, MS, RD, conducted the initial training work shop and served as a consultant. The therapists received supervision every other week.										

Appendix 3.1 ARIADNE study- Tables

Table A3.1 Behavioural content of the intervention

Week(s)	Appointment name	Length	Learning topics and key outcomes
0	Initial consultation	45’	The Dietitian: • introduces themselves and gives an overview of the programme • collects participant history and current medications • assesses motivation and current lifestyle including diet, lifestyle and exercise • problem solves potential barriers • provides education for the TDR stage
1, 2, 4, 6, 8, and 10	Phase 1- Total Diet replacement	15-30’	The Dietitian: • reviews weekly progress, including weight change and any issues with blood pressure and blood glucose, if applicable. • checks product tolerance and usage of fibre supplement • help participant problem solve any issues encountered • ensures ongoing self-monitoring and goal setting continues
12	Wrap-up of phase 1 Phase 2- Food reintroduction	30-45’	The Dietitian: • covers progress summary to close the TDR phase reflecting, by asking questions like: -What went well? -What were the challenges? • reviews total weight loss, blood glucose and blood pressure review • reviews initial goals • explains the phase of food reintroduction • signpost to meal plan resources, cooking methods, and recipes • ensures ongoing self-monitoring and goal setting continues
13, 14	Phase 2- Food reintroduction	15-30’	The Dietitian: • reviews weekly progress including weight change and any

			issues with blood pressure and blood glucose • works with each participant to create and maintain an individualised diet plan • looks at any deviations from dietary protocols and problem solve as required • helps problem-solve as required • ensures ongoing self-monitoring and goal setting continues
15, 17, 19	Phase 2- Food reintroduction II, III	30-45’	The Dietitian: • reviews progress undertaken including achievements, challenges, weight lost, changes in blood glucose or blood pressure • ensures ongoing self-monitoring and goal setting continues
21, 23, 24	Phase 3- Maintenance	15-30’	The Dietitian: • closes the stage of food-reintroduction • assesses against participant’s initial goals • offers guidance on the calculated calorie requirements for the maintenance phase • works with each participant to create and maintain a dietary pattern to sustain weight loss • reviews progress over previous month, help break down any issues/barriers/ lapses, using behavioural change strategies throughout • ensures ongoing self-monitoring and goal setting continues
24	End of programme	15-30’	The Dietitian: • undertake progress review of the last 6 months including achievements, challenges, changes in dietary choices, portions and patterns • revisits initial and evolved goals and expectations

			• helps planning ahead with future goal setting and signpost to local services • ensures ongoing self-monitoring and goal setting continues

Table A3.2 Mean scores per arm across time-points for available data at each point, for the intention to treat population

Outcome and condition	Baseline (n=56)	n	4 weeks	n	12 weeks	n	16 weeks	n	*24 weeks*	n
EDE-Q										
Intervention	3.3 (0.3)	28	3.0 (0.9)	26	2.8 (1.1)	25	2.6 (1.1)	23	2.7 (1.3)	22
Control	3.4 (0.4)	28	3.2 (1.0)	27	3.4 (1.1)	26	3.3 (1.3)	24	3.6 (1.3)	27
EDE-Q Restraint										
Intervention	2.5 (1.1)	28	3.7 (1.2)	26	3.1 (1.6)	25	2.8 (1.5)	23	2.7 (1.2)	22
Control	2.8 (1.4)	28	2.8 (1.4)	27	2.8 (1.6)	26	2.8 (1.6)	24	2.8 (1.8)	27
EDE-Q Weight Concern										
Intervention	3.9 (0.7)	28	3.2 (1.3)	26	2.9 (1.5)	25	2.9 (1.5)	23	2.9 (1.7)	22
Control	3.7 (0.6)	28	3.6 (1.0)	27	3.9 (1.1)	26	3.6 (1.2)	24	4.0 (1.3)	27
EDE-Q Eating Concern										
Intervention	2.1 (1.2)	28	1.5 (1.6)	26	1.6 (1.3)	25	1.4 (1.6)	23	1.7 (1.7)	22
Control	2.7 (1.0)	28	2.4 (1.3)	27	2.9 (1.6)	26	2.6 (1.9)	24	3.3 (1.6)	27
EDE-Q Shape Concern										
Intervention	4.6 (0.6)	28	3.5 (1.3)	26	3.4 (1.6)	25	3.4 (1.7)	23	3.3 (1.9)	22
Control	4.4 (0.7)	28	4.1 (1.2)	27	4.2 (1.3)	26	4.1 (1.3)	24	4.4 (1.4)	27
CIA										
Intervention	22.1 (12.5)	28	15.2 (11.7)	26	16.5 (13.0)	25	15.3 (13.0)	23	14.7 (14.3)	22
Control	18.7 (9.1)	28	21.7 (12.5)	27	23.9 (12.7)	26	22.0 (13.3)	24	25.0 (13.2)	27
PHQ-9										
Intervention	10.9 (6.8)	28			8.0 (6.9)	25			7.4 (5.8)	22
Control	10.7 (5.2)	28			11.6 (6.3)	26			13.0 (7.6)	27
PAID										
Intervention	47.2 (22.3)	28			33.0 (22.3)	25			29.3 (22.3)	22
Control	47.5 (18.0)	28			49.8 (20.1)	26			48.6 (21.0)	27

Table A3.3 Amended questionnaires

The amended version of the EDE-Q will have the following questions omitted:

- Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight (whether or not you have succeeded)?
- Have you tried to exclude from your diet any foods that you like in order to influence your shape or weight (whether or not you have succeeded)?
- Have you tried to follow definite rules regarding your eating (for example, a calorie limit) in order to influence your shape or weight (whether or not you have succeeded)?

The amended version of the CIA questionnaire will have the following questions omitted:

- To what extent have your eating habits/exercising/or your feelings about your eating/shape/weight interfered with meals with family or friends?
- To what extent have your eating habits/exercising/or your feelings about your eating/shape/weight made it difficult to eat out with others?

Appendix 3.2 ARIADNE study- Figures

Figure A3.1 Changes in global EDE-Q scores from baseline to 6 months for intervention and control arm. The dotted lines are individual participants (blue= intervention arm, orange=control arm) and the full line is the mean.

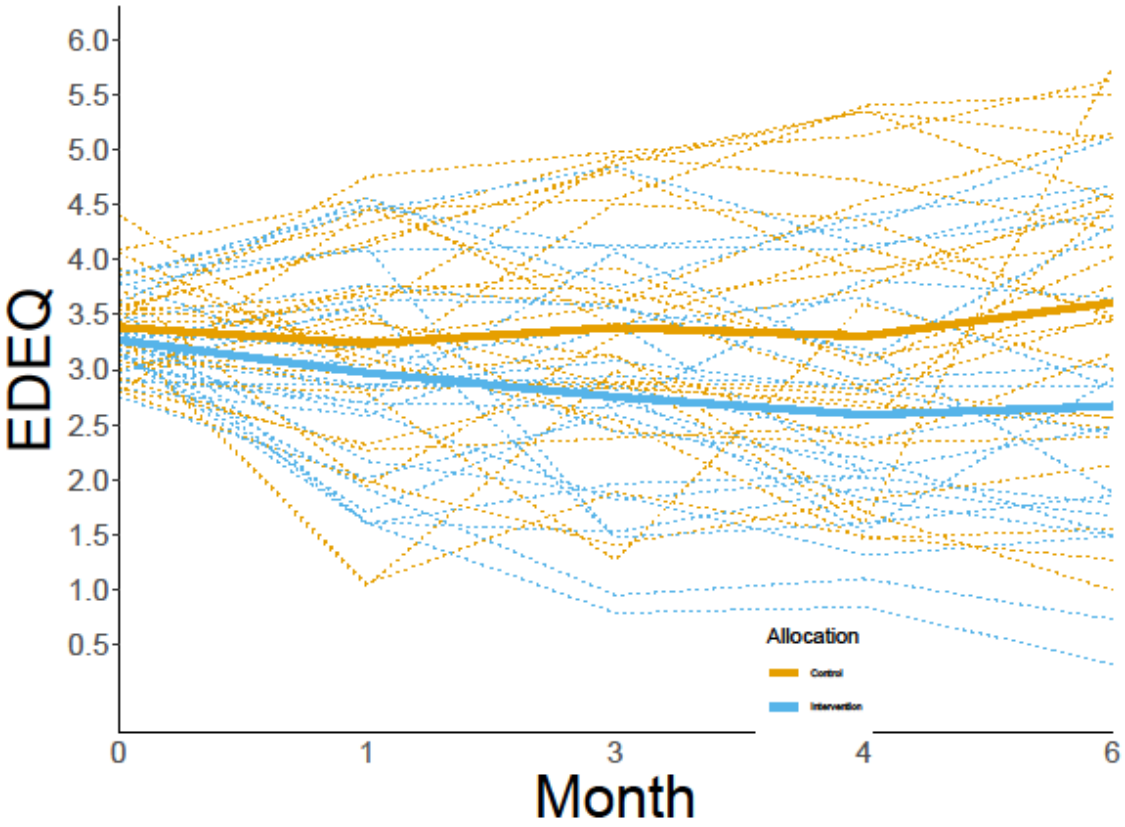


Figure A3.2 Changes in CIA scores from baseline to 6 months for intervention and control arms. The dotted lines are individual participants (blue= intervention arm, orange=control arm) and the full line is the mean.

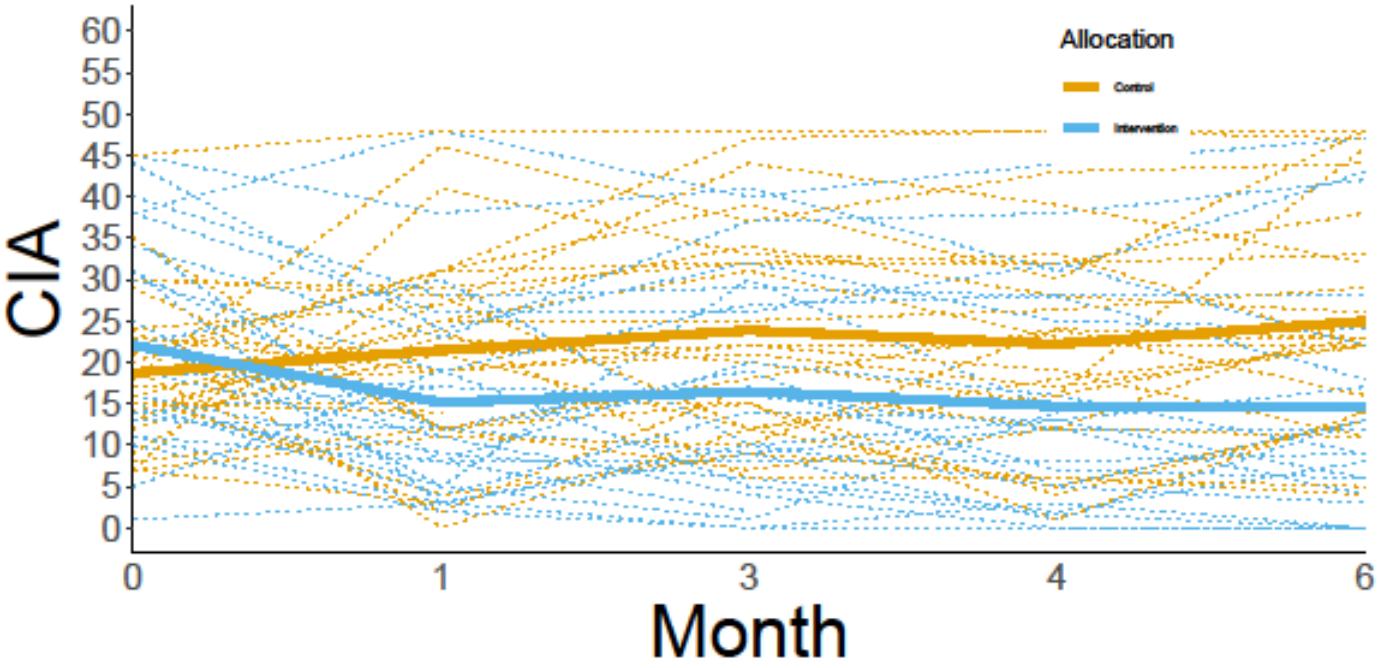
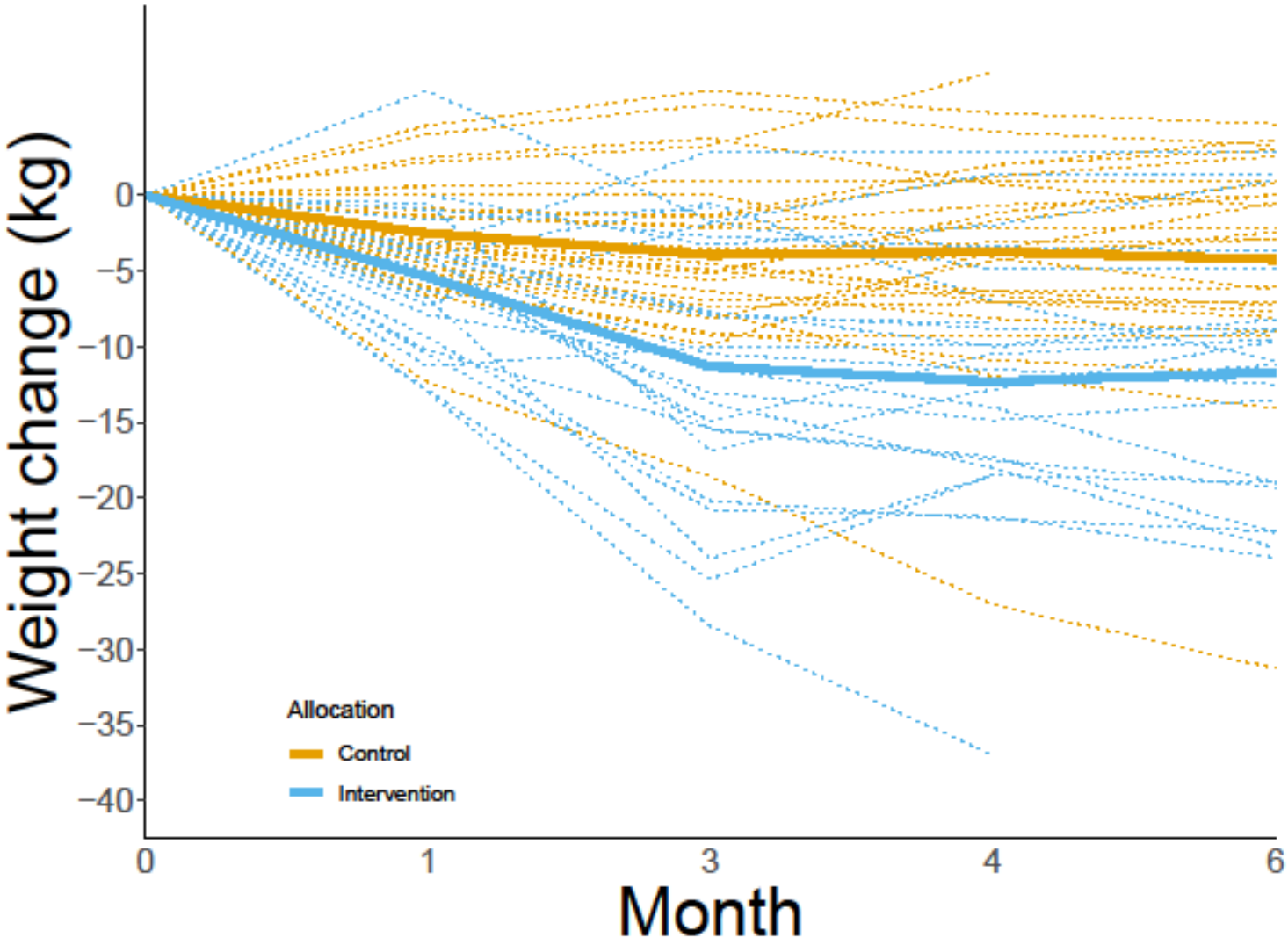
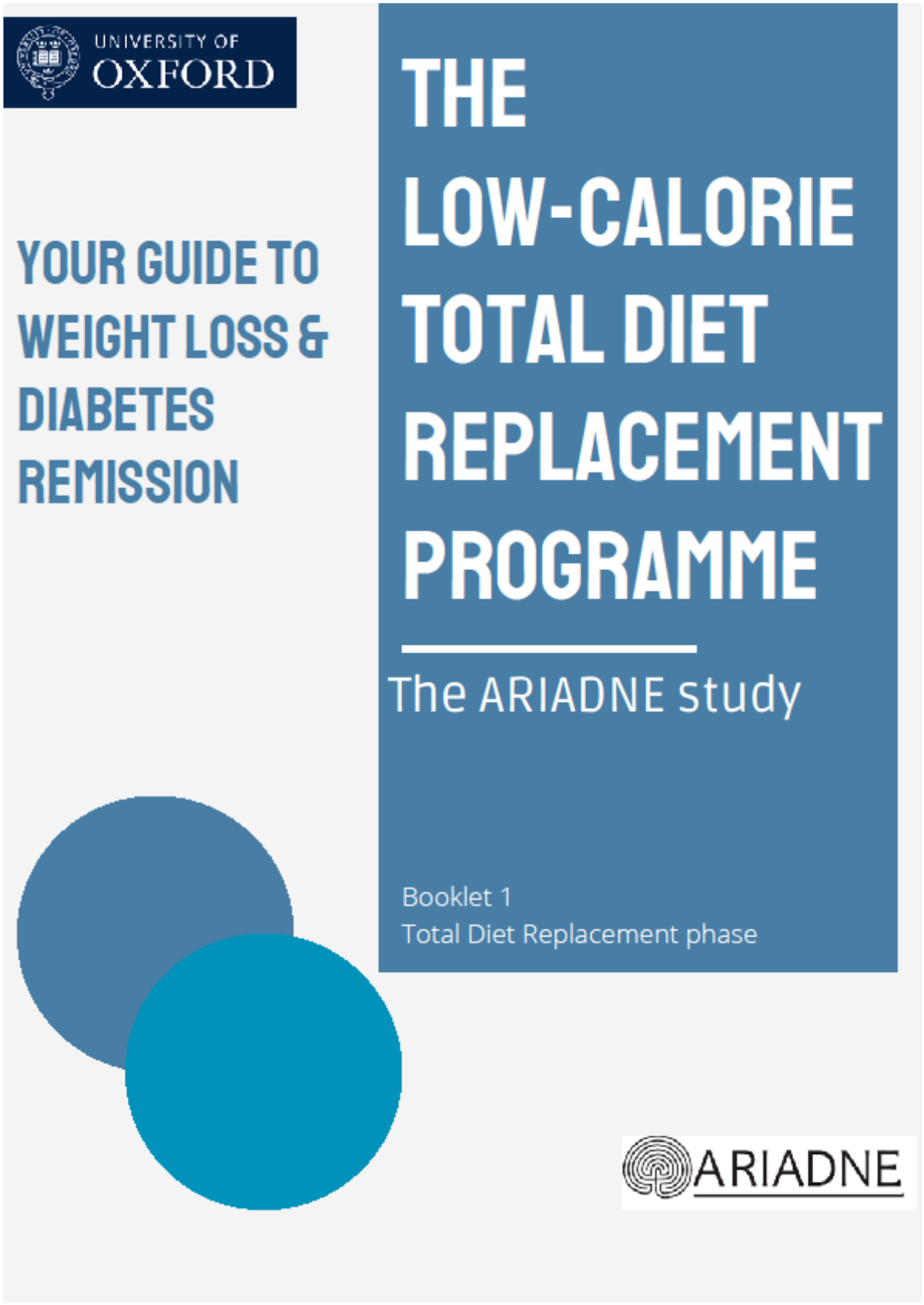


Figure A3.3 Changes in weight (kg) from baseline to 6 months for intervention and control arms



Appendix 3.3 ARIADNE study- Intervention resources



What does the research show and how does it work?

What does the research show?

Based on successful research, the NHS is currently testing a supported weight loss programme for people with type 2 diabetes and overweight.

This research showed that by going on that supported weight loss programme, people can:

- **lose weight**
- **improve their diabetes control**
- **reduce their medication and/or**
- **put their diabetes on remission, by having their blood sugars within healthy range without using medication.**



How does it work?

This programme, called low-calorie total diet replacement, can help people with diabetes lose weight.
This weight loss helps the pancreas better regulate blood sugar.

What is the total diet replacement programme?

The programme consists of three phases:

1. **Total diet replacement (TDR)– 12 weeks**
   You replace all your food with 4 meal replacement products.

2. **Food reintroduction– 8 weeks**
   You will gradually reduce the meal replacement products and introduce healthy meals.

3. **Maintenance– 4 weeks**
   You will focus on developing and maintaining a personalised healthy balanced diet to maintain the weight you lost in the long term.



Throughout the programme, you will be frequently supported by the dietitian.

Overview of the programme

Weeks	Phase	Formula Products	Meals	Fruit
1-12	Total Diet Replacement	4x	-	-
13-14	Food Reintroduction	3x	1x small	1x
15-16		2x	1x small + 1x regular	2x
17-20		1x	2x small + 1x regular	2x
21-24	Maintenance	-	3x regular	2x

Good to know
The above table gives you an idea of how the programme might work for you but you will work with your dietitian to tailor this to your needs and preferences.



Total Diet Replacement phase

You will need to replace all food with 4 TDR products.
This could be any combination of shakes, soups and bars.
Simply mix and match your preferred flavours.

For example, you might choose to have:



I.e a vanilla shake for breakfast, a vegetable soup for lunch, a potato and leek soup for dinner and a chocolate shake for snack in between.

These products are designed to give you all the:
- protein,
- fibre (taken in supplements)
- vitamins
- minerals,
so that you don't need to eat regular foods.

- **You should aim to drink at least 2-2,5 litres of energy-free drinks per day. This could be water, diet soft drinks, diet squash, and tea or coffee, cold or hot.**
- **You can use up to 100 ml of skimmed milk per day in your coffee/tea if you like.**
- **We advise you not to have calorie-dense drinks such as regular soft drinks and alcohol.**

Total Diet Replacement phase

Three points to consider while on the programme:

1. Do your best to follow it.

Starting the programme is a big change compared with your usual diet. People that have followed the programme have said that the first week or so is the most challenging but they find it much easier after that. This is normal as the body adjusts to the diet. Following the diet fully during these first weeks is key to help you follow the programme for the whole 12 weeks.

2. Support is key.

Crucially, the dietitian will support you every step of the way. Having the full support of your family and friends while you are on the programme is also key. You may want to discuss with them ways that they can support you.

3. Make it easier for you.

Removing and avoiding food temptations from your home and workplace, to the extent possible, will help you follow the programme.



Top tips



Prepare each product by adding water first and then the powder. Mix together using a shaker, a whisk or a fork. Use a shaker for best results.



If you like coffee, all sweet shakes can be made with additional 1 or 2 teaspoons of instant coffee (no added sugar).





Add ice-cubes or crushed ice for a cold twist.

Be creative with spices and herbs in the soups.
-Add nutmeg, thyme, oregano, smoked paprika, freshly-ground pepper, curry powder, garlic, crushed chilly.
-Add chopped spring onions, fresh parsley, fresh coriander or chives.





Drinking enough will help you feel fuller and reduce the chance of feeling dehydrated. Choose anything from tap water to shop-bought flavoured water (make sure it's no added sugar) or homemade flavoured water (try adding mint and lemon slices), fruit tea, herbal tea, regular or decaf tea and coffee, sugar-free squash or diet soft drinks.



Plan in advance
If you know you will not be home till late in the evening, bring a bar with you or pack your shakes and/or soups with a shaker and your bottle of water or flask with you to prepare and have on the go.

Top tips



Split the products roughly equally across the day and avoid staying for prolonged periods of time without eating.



Consuming the products slowly can help you feel fuller for longer.
Avoid distractions and be present as much as possible. Give yourself good 15-20 minutes at the end of each mealtime for the brain to receive the message that you are full.



Doing something to distract yourself in case of cravings could help;
Here are a few ideas:
-going for a walk,
-calling someone to talk about something unrelated to food
-playing a game on your phone
-vacuuming or dusting
-gardening.



We eat many times in response to emotions, such as boredom, happiness, sadness, and anxiety rather than because we are hungry. This could be challenging to change during this attempt, so be ready to channel this through an activity or hobby, such as the ones above, when this urge comes.

Is it hunger or thirst? Consider drinking some water, tea or coffee to see if what seems like hunger goes away.



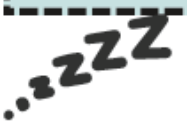
Top tips



It might be useful to avoid cooking shows or watching TV (too many adverts on food!), especially in the beginning. Seeing food being prepared and presented could make it more difficult to follow the programme.



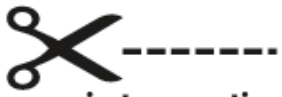
Aim for 8 hours of sleep, if you are not already achieving this. Less sleep than your body needs could lead to feeling hungry more often. Rethink how much sleep you get, why and if this could be improved. Going to sleep earlier might help you avoid feeling hungry.



Overall, most people following this programme report that hunger eventually goes away. The beginning is always the hardest.

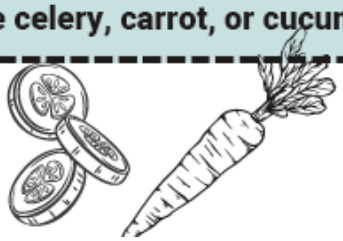


Emptying your fridge and cupboards from foods you know will not be able to resist, will help you avoid temptations, especially in the beginning. Consider donating them to a food bank or give them to friends and family.

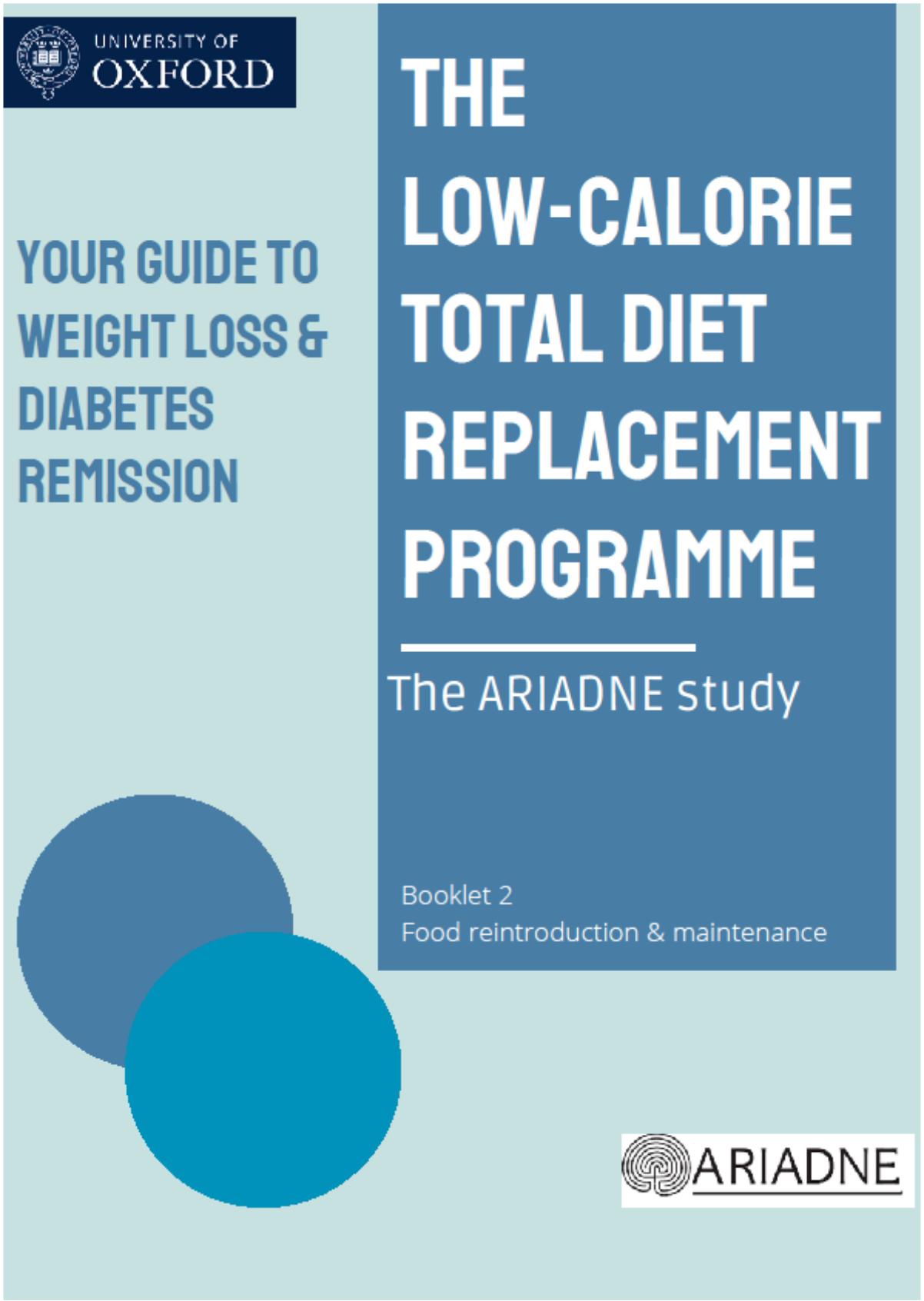


Split your shake or soup in two portions to have in two goes, instead of one. This can make you feel fuller for longer.

Another way to feel full is to have some plain vegetables sticks that will give you a sense of crunchiness like celery, carrot, or cucumber.




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ARIADNE
Booklet 1
Total Diet Replacement phase
October 2022
Do you have any feedback? Let us know!


UNIVERSITY OF
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YOUR GUIDE TO WEIGHT LOSS & DIABETES REMISSION
THE LOW-CALORIE TOTAL DIET REPLACEMENT PROGRAMME
The ARIADNE study
Booklet 2
Food reintroduction & maintenance
ARIADNE

What is the total diet replacement programme?

The programme consists of three phases:

1. **Total diet replacement (TDR)– 12 weeks**
   You replace all your food with 4 meal replacement products.

2. **Food reintroduction– 8 weeks**
   You will gradually reduce the meal replacement products and introduce healthy meals.

3. **Maintenance– 4 weeks**
   You will focus on developing and maintaining a personalised healthy balanced diet to maintain the weight you lost in the long term.



Throughout the programme, you will be frequently supported by the dietitian.

Overview of the programme (again!)

Weeks	Phase	Formula Products	Meals	Fruit
1-12	Total Diet Replacement	4x	-	-
13-14	Food Reintroduction	3x	1x small	1x
15-16		2x	1x small + 1x regular	2x
17-20		1x	2x small + 1x regular	2x
21-24	Maintenance	-	3x regular	2x

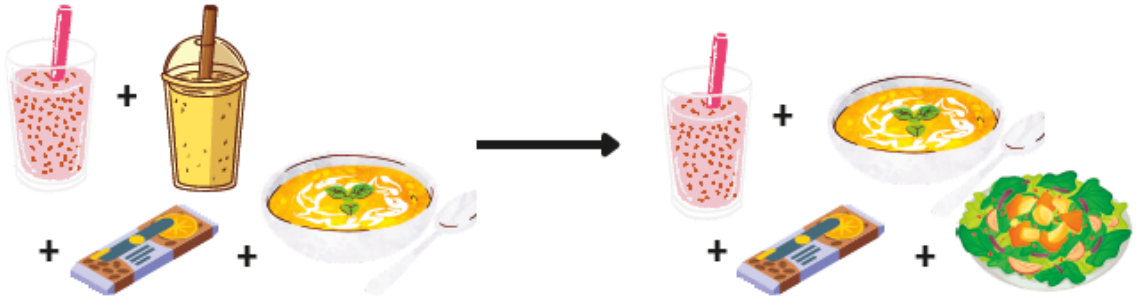
Good to know
The above table gives you an idea of how the programme might work for you but you will work with your dietitian to tailor this to your needs and preferences.



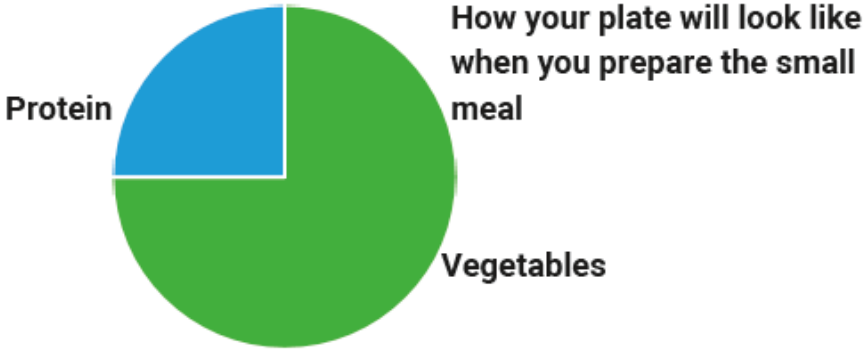
Food reintroduction I phase

You will reduce the meal replacement products from 4 a day to 3 a day and introduce a small meal and 1 portion of fruit (see list D in the next pages).

For example:



The small meal will consist of :
Low fat protein (list A)
+ 3/4 plate of non-starchy vegetables (list B)



You should still aim to drink 2-2,5 litres of energy-free drinks per day.

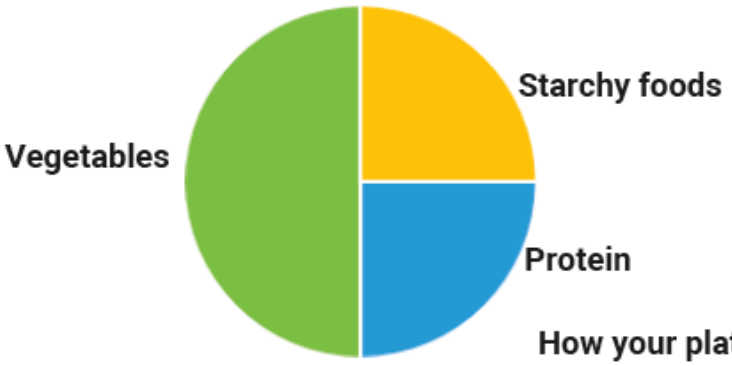
Food reintroduction II phase

You will reduce the meal replacement products from 3 a day to 2 a day and introduce a regular meal and 2 portions of fruit (see list D in the next pages), in addition to the small meal you had at the previous phase.

For example:



The regular meal will consist of :
Low fat protein (list A)
+ 1/2 plate of non-starchy vegetables (list B)
+ 1 portion of starchy foods (list C)



How your plate will look like when you prepare the regular meal

You should still aim to drink 2-2,5 litres of energy-free drinks per day.

Food portions

Low fat protein(list A)

A portion is....

Meat (fat trimmed off), chicken (no skin, white meat)
90 g or a palm

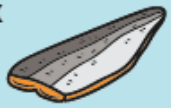


Mince (5% fat)
90 g or 3 medium meatballs



Fish (fillet)
120 g or a fillet

1x



Eggs
2x medium



Quorn sausages
2x



Quorn pieces/mince
200 gr or half a bag



Fat-free Greek yoghurt
150 gr or a small tub



Cheese (low/50% fat)
90 g or 3 matchboxes

3x



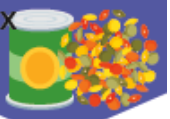
Tofu
125 gr or half a packet

1/2 x



Legumes
half a can or half a cup

1/2 x



Preparation: you can prepare these any way you prefer, but make sure you avoid adding extra calories.
For example, avoid frying or sautéing. You can use a 1-kcal spray to prepare in a pan or roast in the oven.

Non-starchy vegetables (list B)

- Carrot
- Cabbage
- Celery
- Tomato
- Cucumber
- Lettuce
- Leafy greens
- Green salad
- Mushrooms
- Okra
- Green beans
- Brocolli
- Cauliflower

At this stage it's best to avoid the following:

- Potatoes & sweet potatoes
- Sweetcorn
- Peas
- Avocados


Food portions
Starchy food (list C)
A portion is....
Wholemeal bread
2 thin slices
Porridge oats/ wholegrain breakfast cereal
4 tablespoons
4x
Brown pasta (boiled) or rice
1/2 cup or a tennis ball
1x
Potato with skin or sweet potato with skin
1 medium
or
4 baby potatoes (roasted/boiled)
4x baby
1x medium
Quinoa, buckwheat, spelt, millet, freekeh
1 x tennis ball/ half a cup
1x
Cassava chips (baked)
4x or around 60 g
Fufu
100 g or
1/2 tennis ball
1/2 x
DID YOU KNOW?
Wholemeal/brown starchy foods have more fibre than their white equivalents. Likewise, having vegetables and fruit with skin on can also provide more fibre than peeling the skin off.
More fibre in a meal means blood glucose will rise more slowly and stably. It also means that this meal is more likely to keep you full for longer!

Food portions

Fruit (list D)

A portion is....

1x small apple/ pear/ orange



1/2 large or 1 baby banana



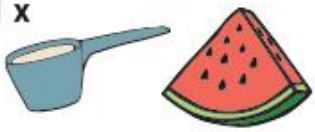
3/4 cup blackberries/blueberries

3/4 x



1 cup watermelon

1 x



2 tangerines



1/2 cup pineapple in juice

1/2 x



1/2 cup mango

1/2 x



1x kiwi



2x medium figs



3 dates



2 tablespoons of dried fruit

2x



Food portions

What about oils and fats?



Oils and fats carry a lot of energy in a small volume.

During the food re-introduction, we recommend using:

- **skimmed milk**
- **reduced fat cheese**
- **0-2% fat yoghurt**
- **remove visible fat from meat and the skin off chicken,**
- **choose cuts with as little fat as possible for your mince (e.g. 5%)**
- **up to 1 teaspoon of oil or butter or seeds per day**





- **Mix 1 teaspoon of oil together with lots of lemon or vinegar to make a dressing**
- **Sprinkle a teaspoon of mixed seeds on your plate**
- **Use 1-kcal spray in cooking**
- **Use baking paper/anti-stick pans**

Food re-introduction III

At this stage, you will start reducing the amount of shakes/ soups/bars from 2 a day to 1 a day and start having one regular meal, two smaller meals and two portions of fruit.
You should still aim to drink 2-2.5 liters of energy-free drinks per day.



Breakfast	Lunch	Dinner	Snack
1 portion of fat-free yoghurt + 1 cup Blueberries (small meal)	1 portion of steak + wilted spinach and lemon juice/oil (small meal)	1 portion white fish steamed + 1 portion brown rice + garlicky green beans (regular meal)	1 vanilla shake + 1 pear
1 chocolate shake + 1 small banana	1 portion chicken breast + green salad with vinegar/oil + 1 portion of boiled baby potatoes (regular meal)	1 portion of tofu + mixed veg (broccoli, carrot, pak choi) with soy sauce into a stir fry (small meal)	1 portion of fat-free yoghurt + 1 cup strawberries (small meal)
1 portion of eggs boiled + 2 slices of brown bread + 1/2 plate cherry tomatoes & cucumber (regular meal)	1 vegetable soup shake + 1 small green salad with lemon juice/oil	1 portion of Quorn sausages + steamed broccoli, cauliflower with lemon juice and garlic (small meal)	1 portion low fat cheddar cheese + 2 dried apricots (small meal)
1 portion of fat-free yoghurt + 1 kiwi (small meal)	1 portion butter beans + mushrooms, carrots, courgettes made into a casserole with mustard and lemon + 1 portion quinoa (regular meal)	1 potato and leek soup	1 portion of low fat feta cheese + 2tbs raisins + carrot sticks (small meal)

Top tips



In the beginning, keep it simple. After 3 whole months of shakes, soups and minimal decision making, you are asked to start having a meal again. This might feel a bit overwhelming in the beginning. Try to keep it as simple as possible.

Meal prep can save time; set aside a bit of time on a day such as Sunday to meal-prep for the week. Choose 2-3 sources of protein and 2-3 different vegetables to accompany your meals in the next few days. Further down the line, include your starchy foods into your meal prep. Plan in advance: if you know you will not be home till late in the evening, pack your shakes and/or soups with a shaker and your bottle of water or flask of tea, as well as your meal(s).





Continue with the previous structure of shakes/soups and only change one thing at a time, if this is easier.

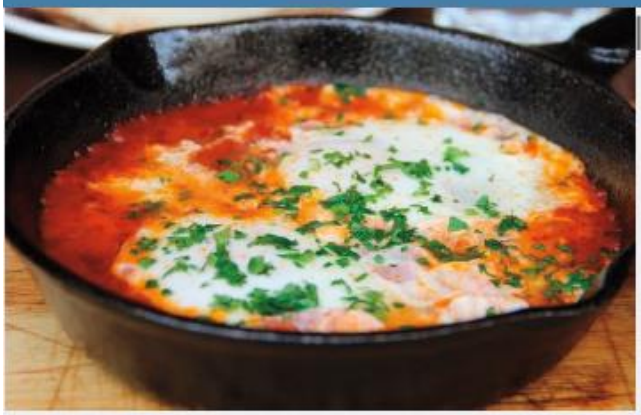


Again, spices and herbs are your friends. Nutmeg, thyme, oregano, smoked paprika, freshly-ground pepper, curry powder, crushed chilly;
they can be added to the newly added meal(s).



Hydration is key. Maintain your fluid intake to at least 2.5 litres a day.

RECIPE SHAKSHUKA EGGS



INGREDIENTS (1 portion)

- 2 eggs
- ½ can chopped tomatoes
- 1 small onion, 1 clove garlic
- ½ bell pepper chopped (optional) Olive oil spray

Spices/herbs:

- ½ tsp garlic powder
- ½ tsp cumin
- ½ tsp crushed chilly (optional)
- handful of chopped fresh parsley or coriander

METHOD

1.Spray 3x times with the oil spray on a non-stick pan and once hot, add the onion, garlic and bell peppers chopped. Fry until onion is browned.

2.Add the chopped tomatoes and the spices, and cook for 5 minutes. Stir occasionally .

3.Crack the eggs on top of the sauce,cover the pan with a lid and leave to cook for 5' or until eggs are done.

4.Serve on a plate and add the chopped parsley or coriander on top.

This recipe for delicious eggs poached in a herby tomato sauce is perfect for breakfast or lunch as a small meal

RECIPE SCRAMBLED TOFU



INGREDIENTS (1 portion)

- 150 g silken tofu crumbled
- 8-10 cherry tomatoes, cut in 4
- ¼ bell pepper
- ½ red onion, chopped
- 1 handful rocket or chopped parsley
- Olive oil spray

Spices:

- ½ tsp turmeric
- ½ tsp freshly ground pepper

METHOD

1. Spray 3x times with the oil spray on a non-stick pan and add the tomatoes, peppers and onion. Fry for 5-10'.
2. Add the tofu and the spices, cook for 2-3'.
3.Remove from the heat and serve on a bed of rocket. Alternatively, you can sprinkle the parsley on top.

This recipe is perfect in the morning
Serves 1 person, as a small meal

RECIPE
FISH PIE



INGREDIENTS (1 portion)

- 60 g Pollock or other white fish, raw
- 60 g prawns, raw
- 120 g cauliflower in small florets
- 120 g butternut squash, peeled and cubed
- ½ small onion
- 2 small salad tomatoes, chopped
- ½ carrot, grated
- Olive oil spray (if needed)
- 2 tsp grated parmesan
- 2 tsp fat-free Greek yoghurt
- Juice from ¼ of a lemon

Spices/ herbs

- ½ a small handful of parsley and 1 sprig of dill or 1tsp of their dry equivalents
- ½ tsp freshly ground pepper

METHOD

1. Steam the cauliflower and the butternut squash until mushy. Mush together and add a small pinchof salt and the pepper.
Add the parmesan.
2. On a non stick pan, dry fry the onion, carrot and spices for 5 min. Add the chopped tomatoes and if too dry, add a splash of water.
3.After 5 min, add in the yoghurt and the herbs and re- move from the fire.
4.Cutthe fish in cubes and add with prawns in a baking dish.
5. Mix with the vegetable mix.
6.Add the mash on top and press even. Drizzle with lemon juice.
7.Bake at 180oC for 20 min and serve.

This recipe is perfect for dinner
Serves 1 person, as a small meal

RECIPE BUTTERNUT SQUASH SOUP



INGREDIENTS (1 portion)

- 240 g peeled and cubed butternut squash
- 80 g mushrooms, chopped
- ½ small onion, 1 clovegarlic
- 400 ml vegetable stock (½ regular cube or 1 low salt cube)
- 2 heaped tbs of fat free yoghurt

Spices/ herbs:

- 1 tsp dried thyme or leaves of 1 spring fresh thyme
- 1 tsp crushed chilly (optional)

METHOD

1. Add the olive oil to a pot and once hot, add the onion, garlic and mushrooms. Fry until the onions are browned.
2. Add the butternut squash and all the spices and herbs.
3. Add the vegetable stock (if using a low salt cube, add a small pinch of salt).
4. Boil until the butternut squash is mushy (check with a spoon) and blitz with a hand mixer.
5. Serve on a plate and add the yoghurt on top.

This recipe is perfect for lunch
Serves 1 person, as a small meal

RECIPE
HEALTHY "FRY-UP" STYLE BREAKFAST



INGREDIENTS (1 portion)

- 1 egg
- 2 rashers back bacon
- 100 g sliced mushrooms
- 2 handfuls of cherry tomatoes or 3-4 salad tomatoes
- 2 thin slices of whole- meal bread

Spices:

- ½ tsp crushed chilly (optional) and/or ½ tsp ground pepper
- Olive oil spray
- Handfuls of fresh spinach or 3 cubes frozen spinach

METHOD

1. Spray 3x times with the oil spray on a non-stick pan and add the bacon, mushrooms and tomatoes for approximately 10 minutes.
2. Move to a plate and on the same pan, spray 2x with the oil spray. Add the eggs whisked, in order to scramble.
3. When ready, move to the plate.
4. Serve with the fresh spinach but if you are using the frozen, microwave on its own for 4 minutes and add to the plate. Serve with crushed chilly and pepper on top (optional)
Enjoy!

This recipe is perfect for breakfast or brunch
Serves 1 person, as a regular meal

RECIPE
OVERNIGHT OATS



INGREDIENTS (1 portion)

- 1 small tub fat-free Greek yoghurt
- 40 g rolled wholemeal oats
- a small handful of fresh or frozen mixed berries (blueberries, raspberries and/or strawberries)
- 1 tbs unsweetened peanut or another nut- butter

Spices:

- 1 tsp cinnamon
- ¼ tsp mixedspice

METHOD

1. Mix all the ingredients together in a bowl or a jar.
2. Put in the fridge and leave overnight.
3. Enjoy in the morning!

This recipe is perfect for breakfast
Serves 1 person, as a regular meal

RECIPE
LENTIL SOUP



INGREDIENTS (1 portion)

- 100 g red lentils, raw or 1/2 can tinned green lentils
- 2 carrots, chopped
- 1 small onion
- 1 clove garlic
- ½ can chopped tomatoes
- 500 ml of vegetable stock (500 ml of water with 1 low salt cube or ½ regular cube)
- 1 tbs olive oil
- 2 tbs fat free yoghurt

Spices/ herbs: 1 tsp cumin,

- 1 tsp turmeric,
- 1 tsp black pepper
- 1 tsp crushed chilly (optional)

METHOD

1. Add the olive oil to a pot and once hot, add the onion and garlic. Fry until the onions are browned.
2. Add the spices and combine into a paste.
3. Add the lentils, chopped tomatoes and carrots.
4. Add the vegetable stock(if using a low salt cube, add a small pinch of salt).
5. Boil for 30' or until lentils are mushy.
6. You can blitz with a hand mixer if you prefer or have it as it is.
Enjoy!

This recipe is perfect for lunch
Serves 1 person, as a regular meal

RECIPE
HEARTY MEATBALLS



INGREDIENTS (1 portion)

- 100 g chicken or turkey mince (raw)
- 80 g sweet potato(cubed, skin on)
- 1 egg
- 1/4 red onion 1clove of garlic
- 1 tsp olive or rapeseed oil
- Handful of cherry tomatoes
- Handful of rocket
- 120 g green beans or runner beans
- Juice from 1/2 lemon

Spices/ herbs:

- 1 sprig of fresh rosemary and 1 sprig of thyme (or 1tsp each dry)
- 1 tsp ground pepper

METHOD

1. In a food processor, add 3/4 of the rosemary and thyme, onion garlic and the egg and whizz well. Transfer to a bowl.
2. Add your mince and pepper in the bowl. Mix well and form small balls.
3.Place the meatballs on a baking tray, using parchment paper
4.Add the sweet potato and coat it using the oil and the rest of the herbs.
5. Cook for about 20' at 200°C.
6. Take the tray out, add the cherry tomatoes and continue roasting for another10 minutes.
7. Steam/boil/microwave the beans for 3-5'.
8. Assemble in the plate, adding the fresh rocket and lemon juice.

This recipe is perfect for lunch or dinner Serves 1 person, as a regular meal

Ready meals

There are also ready-meals you could enjoy instead of cooking. Most supermarkets have their own ranges that could be under 400 kcals. Make sure you read the label!

If the meal is close to 200 kcals, it considered a small meal.
If the meal is close to 400 kcals, it considered a big meal.

Lidl - "Chef select" and "Ready to Cook" – salads and vegetables
M&S – "Count on us", "FullerLonger", or "Balanced for you"
Iceland – "Slimming World"
Sainsbury's - "Healthier Choice","Be Good To Yourself"
Asda - "Fresh Tastes","High Protein"
Tesco – "Healthy Living""Beautifully Balanced"
Aldi - "Specially Selected"salads
Waitrose – "LoveLife" & "Calorie Controlled"
Weight Watchers meals







More inspiration needed?

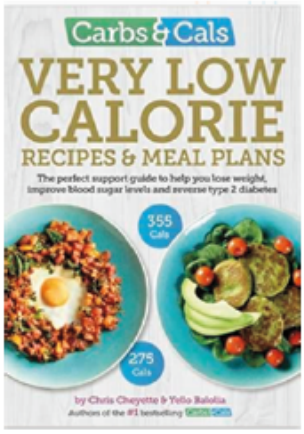


Online

**If you are looking for more inspiration,
check these 200-400 kcal recipes from BBC Good Food:**

**-https://www.bbcgoodfood.com/recipes/collection/400- calorie-meal-recipes
-https://www.bbcgoodfood.com/recipes/collection/200- 400-calories-recipes**

These websites contain over 80 different recipes within this energy content!





Books

**The series Carbs & Cals, that is known for their books on eating with diabetes, has released a book
Full of very low calorie recipes.It can be ordered online.**

Food labels
A brief guide on how to read them

Colour-coded labels on the pack

Most products have a coloured label at the front of pack (typically in a corner with small letters). This shows the amount of total fat, saturated fat, sugar, and salt the product has and whether this is green (low), yellow (medium), or red (high) in them.

Choose mostly products where the majority of the nutrients are green.

Consider products where the majority of the nutrients are yellow.

Limit or avoid the products where the majority of nutrients are red.



Portion sizes matter

The colour-coded label refers to a portion of the food. Most of the time this is significantly less than the whole product. Pay attention to the portion size and consider if the suggested portion is the one you were planning to have. This will help you check the amount of calories, fat, sugar, and salt in your portion.



Maintenance phase
A healthy balanced diet

You have successfully managed to follow the low calorie total diet replacement programme and lose weight; you might feel quite motivated to continue with the weight you have achieved. Some weight gain can happen after finishing the programme, but knowing what to do if this happens can be very helpful!



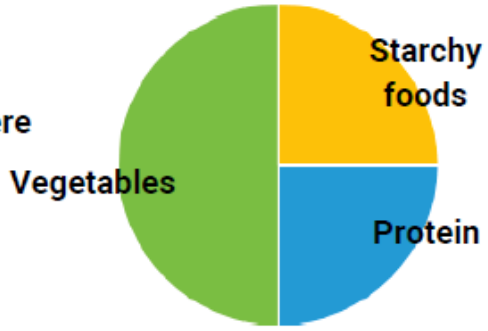
Everyone is different and needs different amounts of energy per day. A balanced diet aims to give you all the nutrients, vitamins and minerals you need for energy and health. Bigger portions and eating more energy than your body needs can contribute to gaining weight.

You can discuss specific future goals and plans with your dietitian.

A generally balanced diet consists of a variety of:

- **Fruit and vegetables**
- **Moderate amounts of wholemeal starchy foods**
- **Protein and dairy**
- **Small amounts of good oils and spreads**

You could follow the plate method showed here to prepare you meals.



Another way of eating could be similar to having 3 "regular" meals and a snack or 2 "regular" and one "small" meals and a snack.
Don't forget your 2 portions of fruit a day!

Maintenance phase
A healthy balanced diet

Tops tips moving forward

Weight yourself regularly
Continue monitoring your weight often (e.g. once a week).



Have another go at the shakes
Take action if you find that you have gained more than 2 kg.
Consider:

- Going back to the total dietary replacement for a period of 2-6 weeks.
- Replace one of your meals with a meal replacement produce for 2-6 weeks.
- Reduce your portions of starchy food and fats and increase the amount of vegetables you eat.



Plan, plan, plan
Planning ahead and cooking meals can be very helpful in your long-term goals.



Experiment
Experimenting with new, healthy recipes can help with repetitiveness and boredom around eating.

Sleeping at least 7-8 hours a day can help you manage your hunger hormones and food intake better.



Maintain a high level of physical activity between 150-300 minutes a week. Any activity counts!



Support
Your family and friends could offer essential help in succeeding your long-term goals, depending on what you find the most challenging

Further resources

Going from seeing a dietitian regularly to managing on your own can be daunting!
Fear not; there are a lot of resources on a healthy balanced diet out there and you have learned lots during the programme.
Your GP and diabetes team can also help if needed.

Some resources that could help are:

- Diabetes UK
  https://www.diabetes.org.uk/guide-to-diabetes/enjoy-food/ eating-with-diabetes/what-is-a-healthy-balanced-diet
- British Heart Foundation
  https://www.bhf.org.uk/informationsupport/support/healthy-living/healthy-eating
- The EatWell Guide
  https://www.nhs.uk/live-well/eat-well/food-guidelines-and-food-labels/the-eatwell-guide/
- British Dietetic Association
  https://www.bda.uk.com/resource/healthy-eating.html
- NHS Better Health- Get Active
  https://www.nhs.uk/better-health/get-active/




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Booklet 2
Food reintroduction and weight loss maintenance
October 2022
Do you have any feedback? Let us know!

Appendix 3.4 ARIADNE study- Study documents

Patient information sheet

ARIADNE

Central University Research Ethics Committee (CUREC) reference: R82152/RE002

ARIADNE study – Key points

Who is this study for?

Adults diagnosed with type 2 diabetes in the last 6 years.

What will I have to do?

You will have a 50-50 chance to be in one of two groups:

Control	OR	Intervention
Carry on as normal		Follow a weight loss programme

- Complete questionnaires online (15-20 minutes)
- 6 times over 1 year
- Measure your weight at home
- We will give you a scale if you don't have one.

What checks are involved?

We will ask you to measure at home and tell us your

- ✓ Weight
- ✓ Blood sugar (if necessary)
- ✓ Blood pressure (if necessary)

as well as your

- ✓ Medication

+ a one-off blood sample using a finger-prick test kit at home (intervention group only)

What is the weight loss programme being tested?

A weight loss programme shown to help people with type 2 diabetes:

- ✓ lose weight
- ✓ reduce their medication

What does the weight loss programme involve?

- Eat only soups, shakes, and bars (formula products) for 12 weeks
- These include all the vitamins and minerals that are essential for good health, but only few calories
- We will give you for free all these products
- Between weeks 13 and 21, you will reduce the number of formula products and gradually start to eat regular food.
- From week 23, you will return to eating only regular food.
- You will have weekly or fortnightly consultations with the dietitian for 15-30 minutes over the phone

Risk and benefits

Intervention

- Your diabetes can go into remission.
- 1 in 2 people go into remission on this programme.
- The more weight you lose, the higher the chances that your diabetes will go into remission.
- This is a big change in the way you eat, and will need commitment on your part and support from the people around you.
- Most people do not experience side effects but some get mild side effects, such as headache, dizziness, or constipation.
- The dietitian will help you maintain motivation and manage side effects if needed.

Usual care

- Your diabetes care will carry on as normal.
- You will continue to benefit from the care your GP provides.
- You will get up to £80 as a thank you voucher for taking part.



How will my data be kept?



- ✓ strictly confidentially and securely
- ✓ in line with the UK General Data Protection Regulations (UK GDPR)

What will happen if I don't want to carry on with the study?



- ✓ You are free to leave the study at any point
- ✓ This won't affect you in any way

What to do if there are problems?



Contact Elena Tsompanaki on ariadne@phc.ox.ac.uk or at 01865289669.

What will happen to the results of the study?



The results will be published but you will not be identified in any publication.

Who funded and approved the study?

Funded by the Novo Nordisk UK Research Foundation. Approved by the University of Oxford Central University Research Ethics Committee (Ref: R82152RE002)

The study flow in a nutshell...

1. Checking you are eligible to take part
(30-40 minutes)

After your read this information, we will ask you to provide consent and complete questionnaires to determine if the study is right for you.
These should take about 30 minutes.
We may send you weighting scales and ask you to confirm your medical history with your GP.

2. Randomisation

If you are eligible, a computer will decide at random whether you will be in the "intervention" group or the "control" group. Your chances to be in either are 50-50.

Intervention

- You will receive the products by post
- You will start the weight loss programme
- Appointments over the phone with the study dietitian
- Consultations over the phone weekly or fortnightly for 24 weeks.
- Self-monitoring blood sugars/ blood pressure at home
- We will give you the monitors if you don't have them

Control Group

- You carry on as normal
- You will continue to receive your care as usual.

3. Week 4
(20-25 minutes)

You will fill in some of the wellbeing questionnaires online.

4. Week 12
(30-40 minutes)

You will fill in all the wellbeing questionnaires, measure your weight at home, report any potential side-effects and your current medication.

5. Week 16
(20-25 minutes)

You will fill in some of the wellbeing questionnaires online.

6. Week 24
(30-40 minutes)

You will fill in all the wellbeing questionnaires, measure your weight at home, report any potential side-effects and your current medication.
Optional audio-recorded telephone interview to tell us more about your experience.

7. Week 52
(30-40 minutes)

You will fill in all the wellbeing questionnaires, your weight, any serious problems (serious/severe adverse events), current medication.
Optional audio-recorded telephone interview to tell us about your experience.

ARIADNE study – Full details

We would like to invite you to take part in our study on low-calorie diet for diabetes treatment and wellbeing.
Before you decide, it is important that you understand why the research is being done and what it would involve for you.
Please take time to read this information, and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please feel free to contact us:
Elena Tsompanaki – Study dietitian
Tel: 01865289669 E-mail: ariadne@phc.ox.ac.uk

What is the purpose of the study?

We want to test how a weight loss programme affect someone's wellbeing. This programme, called total diet replacement, has shown to be very effective in helping people with type 2 diabetes reduce their weight and diabetes medication. It is slowly becoming available across England through the NHS. However, there are still aspects of how it affects wellbeing that are not clear.

Who is this study for?

We are looking for people who have been diagnosed with type 2 diabetes within the last 6 years.

Do I have to take part?

No. Taking part is entirely up to you. You are free to leave the study at any point if you change your mind. The decision to do so will not affect you in any way.

What will happen to me if I decide to take part?

- In the beginning, you will go through the screening process where you will answer questions on your health status, medication and complete questionnaires to determine if this study is right for you. If you are not entirely sure about the answers to some questions, you can speak to the research team. We may ask you to confirm your medical history with your GP.
- If you are not eligible at any stage, we will delete any identifiable data you inserted up until that point and thank you for your time.
- If you are eligible and happy to participate, a computer will place you in either the "control" group or the "intervention" group. You will have 50-50 chance to be in the intervention and 50-50 chance to be in the control.
- You will be asked to repeat some of the questionnaires online at 1, 3, 4, 6, and 12 months (in total, 5 follow-ups). You will need to do these online within the timeframe given. Please see the diagram above ("The study in a nutshell") for details. Depending on the follow-up, these can last from 15 to 40 minutes. These follow-ups happen alongside the intervention (total diet replacement or low calorie weight loss programme for diabetes treatment), for the people randomly assigned to the intervention arm.
- The whole study lasts for a year and will be done completely remotely. You will need internet access to complete the follow-ups online and a telephone to speak with the study team as needed. If you are in the intervention arm, you can choose to have the sessions with the dietitian either via telephone or video call.

What will happen if I am in the intervention group?

Below is an example of how the programme might work, but the exact plan will depend on your personal circumstances and you will work it out it with the dietitian.

Phase 1 Weeks 1-12	You will eat only four formula products per day, such as soups, shakes, and bars. These formula products will provide you with about 880 calories a day in total and will include all the vitamins and minerals that are essential for good health, but only far fewer calories than most people usually eat. We will provide you with these products. You will have sessions with the dietitian every week or other week and these will last between 20-45 minutes, depending on the stage. The dietitian will support you in getting adjusted to the programme. You will measure your blood glucose and your blood pressure (if needed) using monitors we will provide you with, and measure your weight regularly at home. The study doctor will make changes to your diabetes and blood pressure medication, usually by asking you to reduce/stop some or all of the medication on your recurrent prescription. You won't have to go to your GP for any study procedures or changes to medication.
Phase 2 Weeks 13-22	You will have 3 products a day plus a meal of regular food. You will slowly reduce that to 2 products a day and two meals and then to 1 product a day and regular meals. You will have sessions with the dietitian every week or other week and these will last between 15-45 minutes, depending on the stage. The dietitian will support you in moving to eating regular food and help you design an eating plan that is easy to follow and fits your routine. The study doctor will make changes to your diabetes and blood pressure medication.
Phase 3 Weeks 21-24	In the last two weeks, you will return to eating only regular food. You will have sessions with the dietitian every week or other week and these will last between 15-45 minutes, depending on the stage. The dietitian will support you in making long-term changes, so that you can stick to your new eating plan and keep the weight off.

We will audio-record the sessions with the dietitian, with your consent. This is to analyse the transcripts for themes on people's experiences, well-being and opinions about the programme.

What will happen if I am in the control group?

- In the control group, you will continue to benefit from your usual care in your GP practice.
- If you choose to start losing weight either privately, on the NHS, or on your own, you are free to do so, but we will ask you to let us know.
- We might ask some people in the control group to have an interview to share their experiences. This is to understand people's experiences and well-being.

What should I consider?

If you agree to take part in the study, we expect you to:

✓ follow the programme to the best of your ability
✓ respond to the study calls
✓ monitor your blood sugar and blood pressure as advised
✓ measure your weight
✓ and complete all the questionnaires online

We also expect you **not** to:

× be planning to get pregnant, be pregnant, or breastfeeding (females only).
× be taking part in other weight loss programmes at the beginning of the trial.
× be taking part in other studies.

Are there any possible disadvantages or risks from taking part?

- ✓ There are minimal risks from taking part if you are in the control group. Some people might find some questions in the well-being questionnaires triggering or upsetting.
- ✓ Following an intensive weight loss programme can be demanding and needs commitment from you and support from the people around you. Your dedicated dietitian will support you to keep you motivated. The dietitian will also monitor you frequently and carefully, and consult with a specialist study doctor and GP so that you can stop the programme if that is in your best interests. This means that **the likelihood of you suffering an adverse event is low**.
- ✓ In the intervention group, we will advise you to stop all or nearly all medication you may be taking for high blood pressure or diabetes. Because the diet reduces your blood sugar and blood pressure, we advise you to reduce or stop your medication to make sure that your blood sugar or your blood pressure do not drop too low. Changing your medication might also raise your blood sugar or your blood pressure at some point. We will therefore ask you to check this regularly and report the readings to the study dietitian. Based on your readings, we may also advise you to re-start some of the medications at some point. As this intervention has been tested before in people with diabetes, there is extensive guidance on how to change medication and/or doses to support people following the programme.
- ✓ Most people do not experience side effects due to the intervention. About one in five people will experience at least one side effect due to the programme. A few people develop constipation, but we will be providing you with fibre supplements to avoid this, if needed. Less common side effects include fatigue, headache, dizziness, dry mouth, abdominal pain, bad breath, diarrhoea, hair loss, dry skin, mood changes, and feeling cold. Most of these side effects do not pose a risk to your health, are mild, and should go away as you get used to the diet. We will check in each study visit if you experience any of them. Between study calls, you can let us know about them using the contact details at the front of this document.
- ✓ All finger prick tests have a small risk of bruising and pain but are routinely done by people with diabetes who need to measure their blood sugars more closely and we will provide you with guidance on how best to do them.
- ✓ Females only: It is not advisable to become pregnant whilst losing weight, therefore we advise you to use an effective method of contraception for the duration of the programme. If you need more information on effective contraceptive methods, please consult your GP.

What are the possible benefits of taking part?

- Everyone who takes part in this study will be helping us know better how best to help people with type 2 diabetes. Knowing this is one of the main reasons people want to take part in studies. More specifically, the results of this study will help us understand how this programme affects someone's wellbeing. This information can help us shape the treatment of future patients with type 2 diabetes.
- Most people who start the programme lose weight, but how much weight you will lose will depend on how closely you will follow the advice you receive.
- The weight loss may help you to keep being off your diabetes medication.
- The weight loss can also reduce your risk of heart disease.

Will my General Practitioner be informed of my participation?

Yes. We will send 3 letters in total to your GP:

- At the start of the study, to let them know what the study is about and which arm (intervention or control) you have been assigned to

-At 6 months, to update them of your progress

- At 12 months, to update them of your progress and also of the end of the study

Will my taking part in the study be kept confidential?

Yes. Any information that is collected about you during the course of the research will be kept strictly confidential. We will use code numbers to avoid identification of participants with their names. All data will be stored securely on password-protected servers and only the research team will be able to access the information. We will store the pseudoanonymised research data (e.g. questionnaire data,

consultation files) securely at the University of Oxford indefinitely after the end of the study. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

Will I be reimbursed for taking part?

Control group participants: We will compensate you with up to £80 in total. This will be £10 in vouchers each time you complete a follow-up assessment and £15 in vouchers if you are offered an interview, as a thank you for your time. We will also offer you a pre-recorded webinar with the study dietitian in the end of the study, full of dietary tips on how to manage your diabetes and further resources.

Intervention group participants: You will get free food products and dietetic consultations.

What will happen to the samples I give?

If you are on the intervention group, your blood sample will be sent for analysis to an approved third-party provider. After the analysis, they will destroy the sample.

What will happen to my data?

You will provide data for the study using REDCap, a secure online platform.
We will keep all consent forms for 3 years after publication. We will keep identifiable information (e.g contact details) until the end of the study at the University of Oxford, so that we can inform you about the study results. If you opt to allow us to contact you for future studies, we will keep your contact details for 7 years after the end of the study. We will keep a copy of your consent form with this database, as your consent is our legal basis for re-contacting you under UK data protection law.
We will ask you to upload a picture of your prescription or medication online, to ensure we have the right information on your medication. We will delete these as soon as we transfer the information into the study platform.
The dietetic support will be provided by the study dietitian and the de-identified records from the sessions will be kept securely at the University of Oxford indefinitely, as they are usually kept if you go to hospital or your GP. The dietetic sessions and/or telephone interviews will be audio recorded with your consent. We will transcribe some parts of these, using an approved third-party professional transcription company. The selection will be to analyse different changes in well-being, as reflected in questionnaires. The copy of the recording held by the company will be deleted as soon as transcribed. The copy of the recording held by the University will be deleted at the end of the study. We would like your permission to use direct quotations taken from interviews or sessions but without identifying you in any research outputs.
We will keep de-identified research data indefinitely after the end of the study, including demographic, health and medical data, questionnaire responses, and de-identified transcripts.
De-identified data obtained as part of this study may be used in future research, here or abroad, and may be shared with commercial organisations.
Finally, data collected during the study may be looked at by individuals from the University of Oxford where it is relevant to you taking part in this research, for auditing or monitoring purposes.

Data protection

The University of Oxford is the data controller with respect to your personal data and, as such, will determine how your personal data is used in the study.
The University will process your personal data for the purpose of the research outlined above. Research is a task that we perform in the public interest.
Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights .
You can find out more about how we use your information by contacting ariadne@phc.ox.ac.uk.
We will order the products for the programme in the intervention arm through Nestle Health Science, who will receive your name and address to send them to your house. We have signed a contract with the company to ensure they manage this minimal data responsibly and delete them when they finish with their delivery. The company will comply with UK GDPR and the Data Protection Act 2018.

What will happen if I don't want to carry on with the study?

You are free to leave the study at any time without giving a reason. We will give you the opportunity to tell us the reason for leaving. This will not affect you in any way. You can opt to stop the weight loss programme but continue with the follow-ups.

If you withdraw from the study and further communication, we will only use the data collected up to your withdrawal.

What will happen to the results of this study?

The results of this study will be published in scientific journals and presented at academic conferences. We will send you a summary of the results. We will also share the results with organisations helping people living with type 2 diabetes. Anonymous data will be part of the presentations and publications. You will not be identifiable in any presentation or publication. A copy of the thesis will be deposited both in print and online in the Oxford University Research Archive where it will be publicly available to facilitate its use in future research.

What if we find something unexpected?

Filling in questionnaires, measuring your weight, and having a blood test are done for research purposes and not for diagnostic purposes. Therefore, none of our research procedures are substitute for a doctor's appointment. If there is any concern, we will inform your GP and advise you to see them.

Who do I contact if I have a concern about the research or I wish to complain?

If a participant in research is ever considered to have suffered harm through their participation, the University has arrangements in place to provide for compensation. If you have a concern about any aspect of this study, please contact Elena Tsompanaki, ariadne@phc.ox.ac.uk , 01865289669or Professor Paul Aveyard, paul.aveyard@phc.ox.ac.uk, +44 (0)1865 617 860 , and we will do our best to answer your query. We will acknowledge your concern within 10 working days and give you an indication of how it will be dealt with. If you remain unhappy or wish to make a formal complaint, please contact the Chair of the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC) at the University of Oxford who will seek to resolve the matter as soon as possible:

Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7GB.

How have patients and the public been involved in this study?

We discussed this research with people with type 2 diabetes. They helped make sure this study will be done well. They thought this study was trying to answer an important question. In designing this study, we have taken into account their opinions on the study assessments and weight loss programme.

Who is organising and funding the study?

The study is organised by the Nuffield Department of Primary Care Health Sciences at the University of Oxford. The study is funded by the charity Novo Nordisk UK Research Foundation. No personal information about you will be shared with the Novo Nordisk UK Research Foundation. The Novo Nordisk UK Research Foundation will be acknowledged in the publications but will have no role in the design, conduct, analysis, interpretation, writing, and publication of the results.

The products for the programme are bought from the company Nestle Health Science, who will provide them at a discounted price to the research team.

The HbA1c home kit tests will be donated to the research team by the company Medichecks, which will also do the analysis in their laboratory.

Who has reviewed the study?

All research in the University is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed by a subcommittee of the University of Oxford Central University Research Ethics Committee (Ref: R82152/RE001).

Further information and contact details:

Please contact Elena Tsompanaki on 01865289669 or at ariadne@phc.ox.ac.uk .

Appendix 4 ARIADNE study- Qualitative sub-study documents

Figure A4.1 Qualitative interview guide

ARIADNE Semi-structured Interview Guide

Purpose: To evaluate the process of disordered eating score changes throughout the total diet replacement programme for diabetes remission.
Below is a list of topics/questions to be discussed in this study. The qualitative work will remain flexible with respect to participants' agendas but we will cover the broad topics/questions noted. It is common in qualitative work to iteratively develop topics and questions as new ideas develop from early data collection. Therefore, we may add new topics as the interviews progress and data collection continues, as also expected in clinical practice. However, the key topics will explore the purpose stated above.

For intervention arm (the majority is already part of standard weight management questions during dietetic sessions)

1. Introduction. Previous experience of weight loss and body image

- Have you previously tried to lose weight?
- How does your weight affect the way you eat and manage your diabetes?

2. Perception of current programme of weight loss on body image and diabetes

- How do you feel about starting this programme?

3. Experience during the programme

- How are you getting on with the programme?
    - What makes it easy?
    - What makes it difficult?
    - How have your family and friends reacted to you doing the programme?
    - Have you noticed any changes in your mood going from TDR to food reintroduction?
- What is the hardest thing at this stage (e.g. during TDR or food reintroduction)?
  Possible prompt: How is this affecting your wellbeing/mood?
- What are you hoping to achieve from joining the programme?
  Prompt: how important is health to you?
- Have you noticed any changes in your body?
  Prompt: How do you feel about it?

For both intervention group and control group, ad-hoc use

1. Reflecting on the experience of the programme after some time (intervention group, at 12 months)

- How has your experience of the programme been?
- What were your expectations joining this programme?
- Has the programme met these expectations?
- What would you have liked to be different?
  Possible prompt: What kind of support would be helpful to continue your progress or help you address setbacks or challenges?
  Possible prompt: techniques, content, communication, support

- Would you recommend this programme to other people with diabetes?

Possible prompt: People that might think/ manage their diabetes like you

2. Mental health, body image, eating and diabetes (control group, 6 or 12 months)

- Interviewer's name, occupation, role in the study (if needed)
  - How would you describe your mental health/emotions/wellbeing at the moment?

    Possible prompts

    -What is your relationship with food?

    -Has it changed since starting the study/programme?

    -Has anything changed in the way you feel?

    -How do you feel about your weight/body at the moment?
  - How would you describe your eating at the moment?

    Prompt: relevant scores from the EDE-Q/CIA
  - Has anything changed in your eating that has affected the way you feel about your body etc.?
  - What would you like to do at the moment regarding your weight if it was up to you?