National Institute for Health and Care Excellence

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Draft for consultation

Overweight and obesity management: Diet interventions

Economic model report

Clinical Guideline CGxx

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Contents

HE1 Introduction

Body mass index (BMI) has been associated with a variety of diseases and conditions that lead to a large proportion of NHS expenditure and health burden in England. Between 2014 and 2015, it was estimated that obesity-related ill-health was responsible for £6.1 billion of NHS annual expenditure. With this figure projected to increase to £10billion a year by 2050 it is increasingly important to identify cost-effective weight management programmes that can address obesity. Diet interventions have been identified as having the potential to help people living with overweight and obesity to achieve and maintain weight loss.

We have conducted an economic analysis to assess the cost-effectiveness of diet interventions in adults living with overweight and obesity, based on a comprehensive model, PRIMEtime, that links change in BMI with a range of non-communicable diseases (NCDs). In the following sections, we describe in detail how the model is structured and the methods we employed, including all the adaptations made to ensure the model aligns with the NICE reference case and methods.

The clinical review looked at the effectiveness of a range of diet interventions, including total or partial diet replacements, intermittent fasting, plant-based and low carbohydrate diets. After carefully examining the results during the meeting, the committee agreed that total diet replacements appear to be the only diet interventions that showed significant clinical benefits. Therefore, both the economic review and analysis focus on total diet replacements (TDR) only. The clinical review stratified the studies in two main categories: people with diabetes and overweight/obesity and mixed population with overweight/obesity, the latter including people with and without diabetes. This health economics analysis adopted the same stratification.

We identified two health economic studies in the review: 1) Kent 2019[18] used a similarly adapted model from PRIMEtime to assess the cost-effectiveness of a total diet replacement programme for a mixed population who are living with overweight or obesity based on the DROPLET[4] trial and found the intervention to be cost-effective. However, the analysis was based on the first-year results of the trial and had to rely on assumptions regarding weight regain beyond this follow-up. Moreover, the assumptions of its base case scenarios were not entirely aligned to recent NICE economic evaluations that use a higher discount rate of 3.5%.

Xin 2020[30] developed a Markov model to assess the cost-effectiveness of a total diet replacement intervention for people living with Type 2 diabetes from the DiRECT[19] trial and found the intervention to be cost-effective as well. However, new evidence on this population is available and was meta-analysed in the clinical review.

Given the limitations of existing literature, it was agreed to develop a de-novo economic model using the meta-analyses developed for the clinical and a revisited version of the PRIMEtime model. The analysis allowed us to assess the cost-effectiveness of a TDR interventions in people with and without type 2 diabetes and who are overweight or living with obesity.

HE1.1 Decision problem

This analysis assesses whether total diet replacement interventions are cost-effective in England using recently published and unpublished results to estimate weight regain over lifetime. This question was prioritised in the health economic plan as new clinical evidence was recently published, in particular the two UK trials DROPLET and DiRECT, and any change in the recommendation is expected to have a significant economic impact. No clear clinical benefits were identified in the review for other diet interventions included in the research questions, hence this analysis is limited to the total diet replacement programmes, the only showing significant and persistent clinical benefits.

The population of the analysis was stratified in two groups in line with the clinical review: people who have diabetes and a mixed population who are overweight or are living with obesity. In both scenarios, the cost-effectiveness of offering the intervention of people with a BMI above 25kg/m^2 (overweight and obesity) or above 30 kg/m^2 (obesity) was assessed. The control group was usual care defined as conventional diet and standard weight management.

Table 1: Review questions

RQ 2.1	RQ2.1: What is the effectiveness and cost effectiveness of total or partial diet replacements, intermittent fasting, plant-based and low carbohydrate diets in achieving and maintaining weight loss in adults living with overweight or obesity?

Table 2: PICO for review question

Population	People aged 18 years and over who are: • Overweight (BMI 25 kg/m2 to 29.9 kg/m2) or • living with obesity (BMI ≥ 30 kg/m2)
Intervention	Energy restricted diets: • Low energy (total or partial replacement) diets including low energy liquid diets (defined as diet containing 800-1200 calories per day) • Very low (total or partial replacement) energy diets (defined as diets containing less than 800 calories per day) Macronutrient diets: • Low carbohydrate diet (defined as under 130g of carbohydrates) o Very low carbohydrate (defined as under 50g of carbohydrates) Plant based diets with a calorie deficit. (Plant based diets defined as diets excluding meat and fish e.g., vegetarian, and vegan diets). Intermittent energy restriction (patient led fasting) • Time restricted eating: o Intermittent fasting (e.g., 16/8 intermittent fasting) • Alternate day fasting • Fasting for two days (e.g. 5:2 diet) Note: Studies providing support to participants, for example behavioural therapy (behavioural weight management advice, psychological support) and exercise alongside the diets will be included.
Comparator	Primary comparators: o Compared to each other o Usual care defined use of conventional/ balanced diet with calorie deficit (restriction in total energy intake) o No intervention If studies including primary comparators are not identified, studies including secondary comparators will be included: Secondary comparators: • Usual care as defined as: o behavioural weight management advice o General health promotion advice
Outcomes	• Change in weight (kg) or change in BMI from baseline (including % change) • Health related quality of life measured by validated tools

	• Adverse events: o Serious adverse events o Development of eating disorders or disordered eating o Hypoglycaemia o Constipation o Gallbladder problems o Hair loss (transient alopecia) o Hypotension

HE2 Methods

HE2.1 Model overview

A cost-utility analysis was undertaken where lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting including discounting at 3.5% for costs and health effects[20].

HE2.1.1 Populations

The population of the analysis was stratified in two groups in line with the clinical review:

- Adults with type 2 diabetes who are living with overweight (BMI>25 kg/m^2) or obesity (BMI>30 kg/m^2)
- Mixed population of adults (with and without diabetes) who are living with overweight (BMI>25 kg/m^2) or obesity (BMI>30 kg/m^2)

The first reflects the population with type 2 diabetes of DIRECT[19] and DIADEM-I[28] trials where the intervention had the dual objective of reducing weight and putting diabetes into remission. These types of interventions are associated with a higher cost due to stricter monitoring (DIRECT[30, 31]).

The latter represents the mixed population of the DROPLET trial where people with and without diabetes were enrolled [4]. This better reflects the average population in England who are living with overweight or obesity and was included to assess whether offering a TDR intervention to anyone with BMI above 25 or 30 kg/m^2 would be cost-effective in England.

For both populations two different scenarios were tested: one where the intervention was given to people living with obesity (BMI>30 kg/m^2) and one where people were living with either overweight or obesity (BMI>25 kg/m^2).

A further stratification based on ethnicity was initially proposed as the model can be adapted to use a different minimum theoretical risk for people whose risk of diseases is affected by lower or higher level of BMI (see also section HE2.4.2.2 on minimum theoretical risk). However, not enough data were available to estimate baseline characteristics of people with a particular ethnicity and so this stratification analysis was dropped.

HE2.1.2 Interventions

The following comparators were included in the analysis:

- Low energy total diet replacement (TDR) (800-1200 calories per day) plus support
- Usual care (advice)

The interventions were fairly similar across the three trials used to inform this analysis. In DIRECT, a low-energy formula diet (825–853 kcal/day; 59% carbohydrate, 13% fat, 26% protein, 2% fibre) was given for a period of 3 months followed by structured food reintroduction of 2-8 weeks[19]. In DROPLET trial, participants replaced all food with formula food (810 kcal/day) for a period of 8 weeks followed by a 4-week stepwise reintroduction of conventional food[4]. Finally, in DIADEM-I people underwent a 12-week total diet replacement phase, in which they were given the same formula used in DROPLET followed by a 12-week structured food reintroduction phase[28].

All three studies had an important support component that was found to have a pivotal role in ensuring that the weight loss would be maintained after the end of the diet. DROPLET[4] trial

included a stepwise reintroduction of conventional meal after the intervention while providing behavioural support and encouraging participants to attend monthly appointments. DIADEM-I[28] participants were supported by a team of trained dietitians, personal trainers, and physicians during both intervention and food reintroduction phases. Finally, DIRECT participants were followed-up by dieticians and practice nurses in a structured maintenance support with short "rescue plans" offered to people with great weight regain[19]. Usual care was defined as best-practice care in accordance with guidelines (DIRECT), practice's usual weight management protocol (DROPLET) or standard diet and activity advice (DIADEM-I).

The clinical review did not find any significant and long-lasting clinical benefits for the other diet interventions included in the protocol such as intermitted fasting or partial meal replacement, hence the economic analysis was limited to low-energy total diet replacements only, which showed a clear and sustained weight loss.

HE2.2 Model structure

The model consists of three main modules:

1. A BMI distribution model which is used to estimate the effect of weight loss and weight regain on lifelong BMI trajectories
2. Eight Markov models that calculate lifetime incidence of diseases based on the new level of BMI. These diseases are: diabetes, ischemic heart diseases (IHD), stroke, breast cancer, colorectal cancer, kidney cancer, pancreatic cancer and cirrhosis (see Table 3). These Markov models are independent so they do not take into account comorbidities or interactions between diseases (see HE3.3.3)
3. A life table module was used to estimate final outcomes using differences in QALYs, mortality and costs derived from the Markov models

Table 3: Diseases included in PRIMEtime

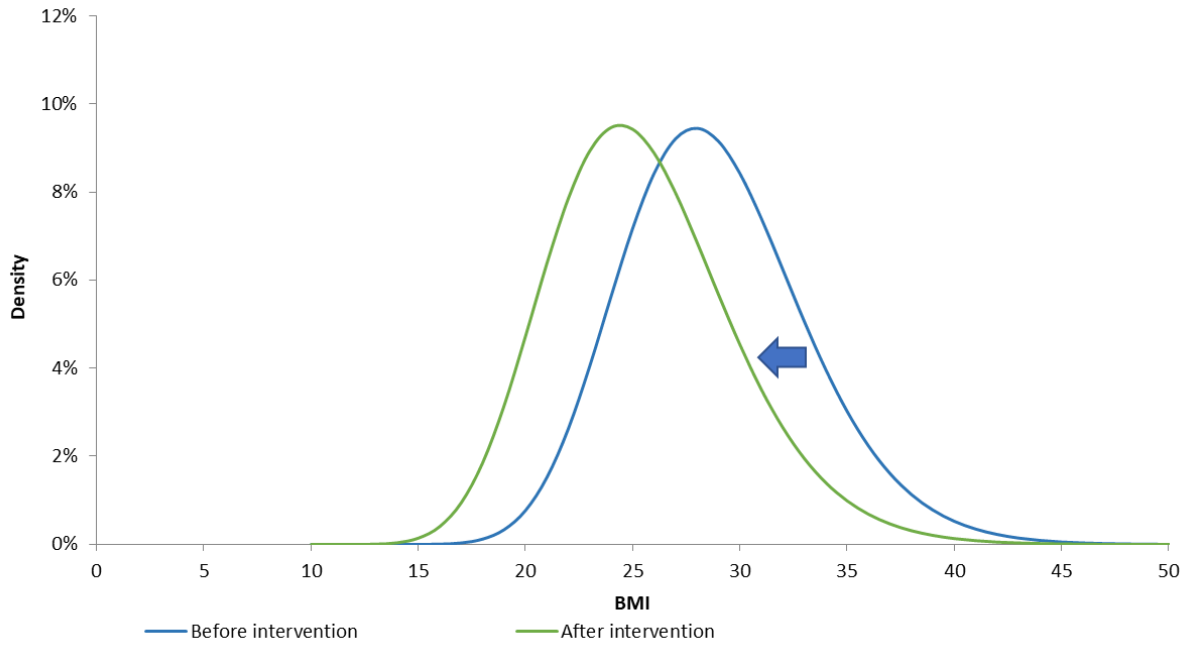
Cardiovascular diseases	Metabolic disorder	Cancer	Liver disorder
Ischemic heart diseases (IHD)	Diabetes	Breast cancer	Cirrhosis
		Colorectal cancer	
Stroke		Kidney cancer	
		Liver cancer	

A set of inclusion criteria were defined by the original developers of PRIMEtime to decide which type of diseases to be included in the model[24]. The criteria were as follows:

1. Evidence for the relationship between risk factors and health outcomes must be shown in a meta-analysis of either prospective cohort studies or randomised controlled trials, with an effect size significantly different to the null hypothesis ($P < 0.05$)
2. The relationship must not be a comparison of "high risk" versus "low risk" groups, where the level of exposure in high and low risk groups is ill-defined.
3. The health outcome must be a NCD (e.g., relationship between BMI and falls are not included).
4. The health outcome must make a substantial contribution to NCD mortality (greater than 500 mortalities in the UK)

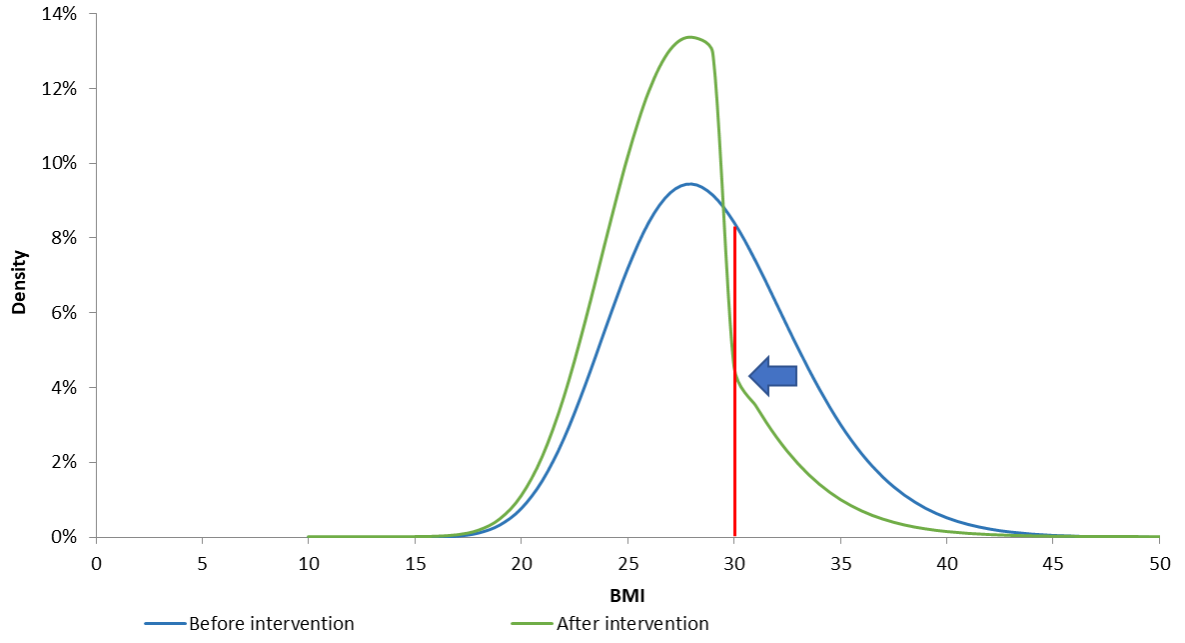
The first part of the model is used to calculate the new BMI trajectories taking into account the weight loss in the short run (between 1 and 3 years) and weight regain in the long run (see also section HE2.4.3). The original PRIMEtime model was mainly developed for population-level interventions (Figure 1). In this type of intervention, the entire BMI distribution shifts to left as it is assumed that people at each BMI level are affected.

Figure 1: BMI distribution with a population-level intervention.



For our purpose, the model was adapted for the evaluation of interventions targeting specific groups (e.g. people who are living with overweight or obesity), as illustrated in Figure 2. The baseline characteristics, such as disease prevalence and mortality, were all adjusted to reflect the targeted population (see also **Error! Reference source not found.**).

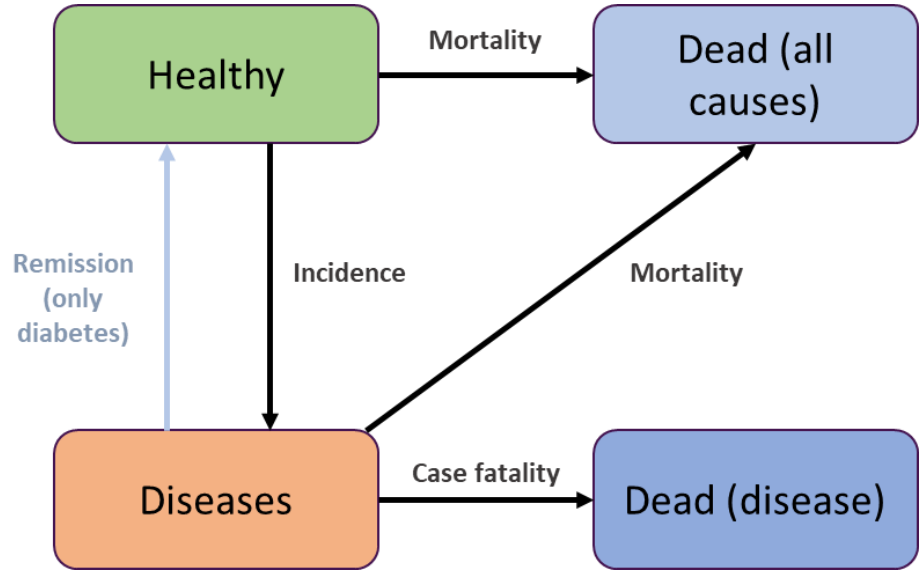
Figure 2: BMI distribution with a targeted intervention



The red line represents the cut-off identifying people received the intervention (i.e. people with a BMI > 30). People in the model are divided in 11 different groups defined by their BMI (<15, 15 to <20, 20 to <25, 25 to <30, 30 to <35, 35 to <40, 40 to <45, 45 to <50, 50 to <55, 55 to <60, 60+). Changes in BMI following weight reduction are calculated separately for each category using group-specific average height and BMI. New incidence for any disease is then calculated using the formulas illustrated section HE2.4.2.3.

Once the new BMI trajectory is defined and new incidence rates are calculated, a series of Markov models are utilised to calculate differential prevalence and mortality. The structure of the models is illustrated in Figure 3.

Figure 3: Natural history of diseases Markov model

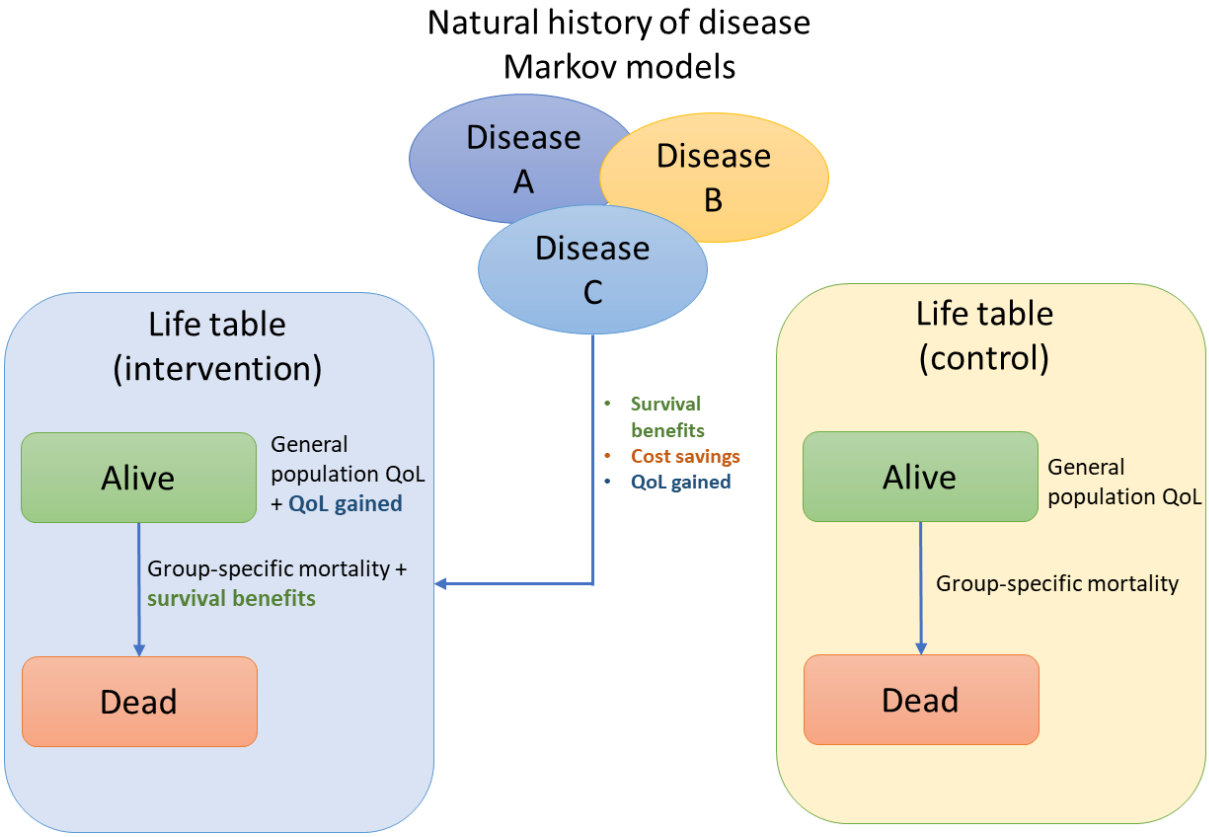


People start in either the healthy or disease state in a proportion defined by the prevalence of each disease in the population of interest. The baseline prevalence and proportion for the general population were adjusted for people with BMI > 25 kg/m^2 and BMI > 30 kg/m^2 (see section HE2.4.1.2). Everyone is at risk of dying for general causes although people in the disease state have an increased risk of mortality caused by disease-specific case fatality.

At each cycle, people can move from the healthy state to the disease state with the incidence/risk defined by their BMI level. People who received the intervention would be subject to a lower risk during the period of time weight loss is maintained, which will lead to a persistent difference in prevalence and mortality between the intervention and control groups. Transition from the disease to the healthy state, or remission, is allowed for one of the modelled diseases, type-2 diabetes, as DiRECT trial[19] collected information on remission from diabetes (see also section HE2.4.3.3 on remission). All the other diseases are assumed to be permanent. In the sensitivity analysis, remission from diabetes was excluded to align the model to previously published PRIMEtime analyses that did not allow remission from any disease. While in the disease state, people incur healthcare cost which is calculated either per incidence (transition cost), for diseases characterized by high immediate costs (e.g. surgery), and per prevalence (state cost) for those that have long-term management costs (see section HE2.4.4.2). People in the disease states also experience impaired quality of life with a disease-specific disutility factor obtained from the literature (see section HE2.4.5).

The natural history Markov models are used to calculate differential healthcare costs, quality of life and mortality between the intervention and control groups, for each disease separately. These are all fed into the life table module to estimate final outcomes in terms of incremental QALYs and mortality (see Figure 4). Whereas people in the control life table have general population quality of life and group-specific mortality (see also section HE2.4.1.3 on mortality adjustment), people in the intervention life table benefit from lower mortality, healthcare cost savings and higher quality of life as determined by the calculations from the Markov models for each disease.

Figure 4: Natural history of diseases models and life tables



The life tables are then used to calculate lifetime costs and QALYs. A half-cycle correction was applied to use the number of person-years at each cycle. The model is run until the cohort reaches the age of 100 (50 cycles in the base case scenario) to estimate lifetime costs and outcomes. A discounting factor of 3.5% was used as per NICE reference case[20].

HE2.3 Model parameterisation

Identifying sources of parameters

Weight losses at 1 year and further follow-ups came from the systematic review conducted for this research question. Extrapolation on weight regain over lifetime was done in R studio and based on the observed datapoints (covering 1-3 years) and 5 years academic-in-confidence data from DIRECT. A second scenario with a more conservative assumption using a 5-year linear weight regain was included.

Most of the parameters of the original PRIMEtime model developed by the Nuffield Department of Population Health at Oxford University were maintained, with some noticeable exceptions:

- BMI distribution in the UK population as well as gender split and average age were collected from the most recent Health Survey for England (HSE) database 2019. HSE is a survey conducted each year covering a range of characteristics including socio-economic, demographic and health indicators. BMI and other important health indicators in the survey were not self-reported but instead collected during a follow-up visit conducted by a nurse, which improved the reliability of these measures[15].

- Diseases prevalence in people with BMI > 25 kg/m^2 and BMI > 30 kg/m^2 was adjusted using data from HSE 2016-2019
- EQ-5D-3L utility score in the general population was estimated using the ALDVMM model described the latest DSU report[14]
- The cost of each disease was updated using the methodology described by Cobiac et al.[8]
- Incidence, prevalence and case fatality were updated to the most recent data using the Burden of Disease database restricted to the UK[12]

HE2.4 Parameters

HE2.4.1 Population parameters

HE2.4.1.1 Initial BMI distribution

Demographic and BMI distribution of the English population were estimated using the most recent version of the HSE 2019. BMI was separately calculated for each gender and age group (see Table 4). In the base case-scenario, a cohort of 50 years old people almost equally split between women (54%) and men (46%) were chosen. Both the starting age and gender split reflect mean demographic characteristics of the cohort in the HSE 2019.

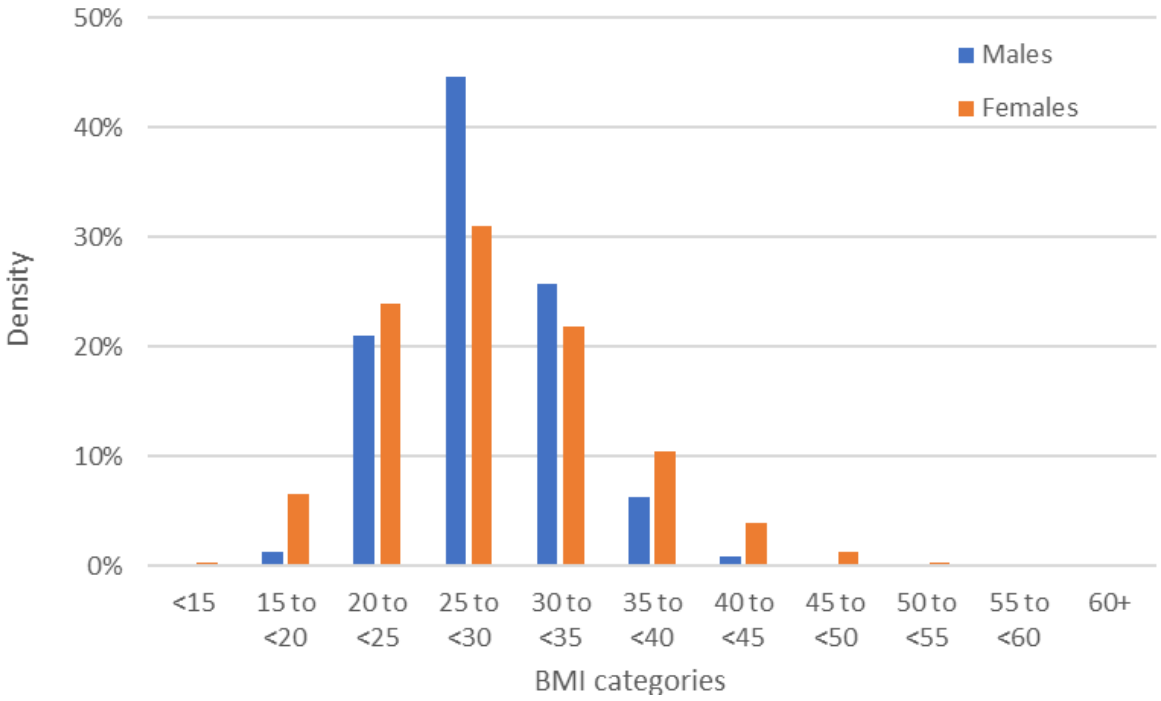
Table 4: BMI by age and gender

Age	Male	Female
16-20	24.1 (5.7)	24.5 (6)
20-24	25.6 (5.6)	25 (5.9)
25-29	26.4 (5.2)	27.5 (6.9)
30-34	27.2 (4.9)	27.5 (6.9)
35-39	28.0 (5.3)	27.7 (6.6)
40-44	27.5 (4.6)	28.4 (6.7)
45-49	28.8 (4.6)	28.7 (6.3)
50-54	28.4 (4.3)	28.8 (6.6)
55-59	29.1 (5.2)	28.3 (6.1)
60-64	28.7 (4.8)	28.3 (6.2)
65-69	29.3 (5.3)	28.1 (6)
70-74	29.2 (4.7)	28.1 (5.5)
75-79	28.2 (4.4)	28.1 (5.8)
80-84	27.4 (3.6)	27.4 (5.1)
85-89	26.3 (3.4)	27 (4.7)
90+	26.0 (2.2)	27 (4.6)

Source: HSE 2019[15]. Mean BMI with standard deviation in brackets

Age and gender-specific BMI distributions were calculated assuming that BMI would follow a lognormal as confirmed by empirical studies[25]. The model assigned people to eleven different BMI categories ranging from below 15 to above 60 (see Figure 5)

Figure 5: BMI distribution in males and females aged 50



The effect of BMI on the incidence of the diseases was estimated for each BMI and gender category using its midpoint BMI, e.g. 27.5 for people in the BMI group 25-<30 (see also section HE2.4.2.3 on incidence calculation).

HE2.4.1.2 Adjusting prevalence

Age- and disease-specific incidence, case fatality rates and baseline prevalence for the general population were derived from the Global Burden of Disease (GBD) study and were calculated using the *Disbayes* package for R studio[21]. As the model was run separately for people with BMI above 25 kg/m ^{2} and 30 kg/m ^{2}, baseline prevalence rates were adjusted for these two populations to reflect the fact that people who are living with overweight or obesity have higher disease prevalence than the general population. Published HSE data from three consecutive years (2016-2019) were used to adjust the baseline prevalence for the targeted population. Except for cancer, all the diseases included in the models are reported in one or more HSE rounds, so the association between weight status and prevalence could be established. As cancer was not recorded in any round of the HSE, its prevalence could not be adjusted for high levels of BMI. However, cancer is a relatively rare disease with a very low baseline prevalence, so the adjustment was not expected to impact the results of the model in a significant way.

A modified Poisson Regression firstly described by Zou was used[33]. Poisson regression is generally regarded as appropriate for analysing rare events (such as diseases) although it is known to overestimate the error of the relative risk when applied to binomial data. Zou proposed a Poisson regression with a sandwich (robust) error term that has proven to be as flexible and powerful as binomial regressions while having the advantage of estimating relative risk instead of the odds ratio of a logistic regression. This approach has been successfully used in similar analyses on obesity and alcohol use[11]. An adjusted regression approach was used with obesity or overweight status as independent or explanatory variables and presence or absence of disease as the dependent variable. We also controlled age in the model to account for age-related differences in the prevalence of obesity. No further control was deemed necessary as the purpose of this analysis was not to determine the causal effect of BMI on diseases but to adjust prevalence of the included diseases among those who are living with overweight or obesity. The regression was run separately

for females and males and for the two BMI categories (>25 kg/m^2 and >30 kg/m^2) using Stata 13.1[26]. The results are illustrated in Table 5 for people living with obesity (>30 kg/m^2) and in Table 6 for those who are living with overweight or obesity (>25 kg/m^2).

Table 5: Prevalence rate ratio of having the disease with BMI >30 kg/m^2

Disease	Males	Females
Diabetes type 2	2.23 (0.15)	2.61 (0.18)
IHD	1.44 (0.20)	1.32 (0.25)
Stroke	1.54 (0.32)	1.19 (0.29)
Cirrhosis	1.40 (0.59)	1.39 (0.62)

Note: Prevalence relative risks (PRR) approximated from the Prevalence Rate Ratio of the Poisson model. PRR calculated comparing exposed (BMI >30 kg/m^2) and non-exposed (BMI <30 kg/m^2) people. Robust standard errors in parentheses. The regression was controlled for age.

Table 6: Prevalence rate ratio of having the disease with BMI >25 kg/m^2

Disease	Males	Females
Diabetes type 2	1.95 (0.19)	3.36 (0.36)
IHD	1.40 (0.25)	1.88 (0.44)
Stroke	1.07 (0.26)	1.01 (0.25)
Cirrhosis	2.06 (1.16)	1.72 (0.88)

Note: Prevalence relative risks (PRR) approximated from the Prevalence Rate Ratio of the Poisson model. PRR calculated comparing exposed (BMI >25 kg/m^2) and non-exposed (BMI <25 kg/m^2) people. Robust standard errors in parentheses. The regression was controlled for age.

A prevalence rate ratio or prevalence relative risk (PRR) provides an estimate of the increased prevalence of the disease among exposed individuals compared with non-exposed individuals. Table 5 and Table 6 show that BMI levels above 30 kg/m^2 or above 25 kg/m^2 are associated with a higher prevalence of the diseases modelled. This is particularly evident for diabetes: people with BMI over 30 kg/m^2 are twice more likely to have diabetes compared with non-obesity population. On the other hand, the prevalence of stroke hardly increased among people with BMI above 25 kg/m^2 although a higher prevalence was found in people with BMI above 30 kg/m^2.

To calculate the disease prevalence among people who are living with overweight or obesity (the exposed), we need to first calculate the disease prevalence among individuals with normal weight (non-exposed) using the following equation:

$$P_{Non-exposed} = \frac{P_{general\ population}}{(1-x) + xPRR}$$

where $P_{general\ population}$ is the disease prevalence in the general population, x is the prevalence of overweight/obesity and PRR is taken from Table 5 or Table 6. Once the disease prevalence in the non-exposed population is known, the prevalence in the overweight/obesity population can be estimated by applying the corresponding PRR to $P_{non-exposed}$. This was done separately for people who are living with overweight or obesity and for each gender.

HE2.4.303 Adjusting mortality

Mortality in the general population was estimated using ONS life table 2017-2019[1]. More recent life tables were available but not used to avoid the increased mortality rates during the COVID pandemic period, which could lead to an overestimation of the long-term mortality rates in England.

Similar as the disease prevalence discussed above, mortality rates were also adjusted for people with BMI over 25 kg/m^2 and 30 kg/m^2, as these two population groups (particularly the latter one) have more comorbidities and therefore higher mortality than the general population. As a first step, data on case fatality (from the GBD study[21]) and disease prevalence (see HE2.4.1.2) were used to calculate the 'disease-free' mortality rate (M_0) that excludes the mortality attributable to the diseases included in the model:

$$M_0 = M_{general\ population} - \sum (P_{general\ population} \times CFR)$$

where $M_{general\ population}$ is the all-cause mortality in the general population, and $P_{general\ population}$ and CFR are the prevalence and case fatality (from GBD) of a particular disease included in the model, respectively. The last bracket in the equation represents the mortality attributable to a particular disease, i.e. the proportion of deaths directly caused by the disease. It was calculated for each disease in the model, summed together and then subtracted from the all-cause mortality in the general population to calculate the 'disease-free' mortality M_0, which represents the mortality rate of a hypothetical population not affected by any modelled disease. Once this 'disease-free' mortality was calculated, mortality rates in those whose BMI over 25 kg/m^2 or 30 kg/m^2 were adjusted using case fatality and the disease prevalence among these two populations through the following equation:

$$M_{obese} = M_O + \sum (P_{exposed} \times CFR)$$

where $P_{exposed}$ is the adjusted disease prevalence among people who are living with overweight or obesity, as calculated in HE2.4.1.2. The calculations were done separately for people whose BMI over 25 kg/m^2 or 30 kg/m^2 to obtain two different mortality rates for these two population groups.

Using the model above, we estimated a mortality hazard ratio (HR) for people living with obesity compared to people with healthy weight (BMI <25 kg/m^2) of 1.2. This figure is lower than the reported HR from a Lancet review of prospective studies[12], 1.45, but still within the confidence intervals estimated by the Framingham Heart Study[32]: 1.14 to 1.41. This highlights a major limitation of disease-based models: they can only capture mortality caused by the diseases included in the models but fail to account for deaths caused by other diseases or other consequences of BMI (see section HE3.3.3).

HE2.4.2 BMI and incidence of diseases

HE2.4.2.1 Relative risks

The relative risks (RR) used in the model to estimate the relationship between BMI and non-cancer diseases were taken from the Prospective Study Collaboration systematic review [12], a meta-analysis of 57 prospective studies including 894,576 participants, mostly in Western Europe and North America. The analysis was adjusted for age, sex, smoking status, and further corrections were made to limit reverse causality. To estimate the relationship between BMI and incidence of cancers, another meta-analysis on 141 prospective observational studies was used[23], which included 283,137 incident cases of cancer. Table 7 illustrates the relative risks used in the model from the two above mentioned meta-analyses.

Table 7: Relative risks

Disease	Unit of change	Relative risk	Source
Diabetes	5 kg/m^2 increase	BMI 15–25: 0.96 (0.25) BMI 25–50: 2.16 (0.07)	Prospective Study Collaboration[12]
IHD	5 kg/m^2 increase	Age 35–59: 1.50 (0.04) Age 60–69: 1.40 (0.03) Age 70–79: 1.31 (0.03) Age 80–89: 1.30 (0.05)	
Stroke	5 kg/m^2 increase	Age 35–59: 1.76 (0.08) Age 60–69: 1.49 (0.06) Age 70–79: 1.33 (0.06) Age 80–89: 1.10 (0.08)	
Cirrhosis	5 kg/m^2 increase	BMI 15–25: 0.73 (0.16) BMI 25–50: 1.79 (0.08)	
Liver cancer	5 kg/m^2 increase	Age 35–79: 1.47 (0.08)	Renehan et al. 2008[23]
Breast cancer[(a)]	5 kg/m^2 increase	Age 60+: 1.12 (0.02)	
Colorectal cancer	5 kg/m^2 increase	Men: 1.24 (0.02) Women: 1.09 (0.02)	
Kidney cancer	5 kg/m^2 increase	Men: 1.24 (0.04) Women: 1.34 (0.03)	

a) Increased risk of breast cancer due to BMI only for women

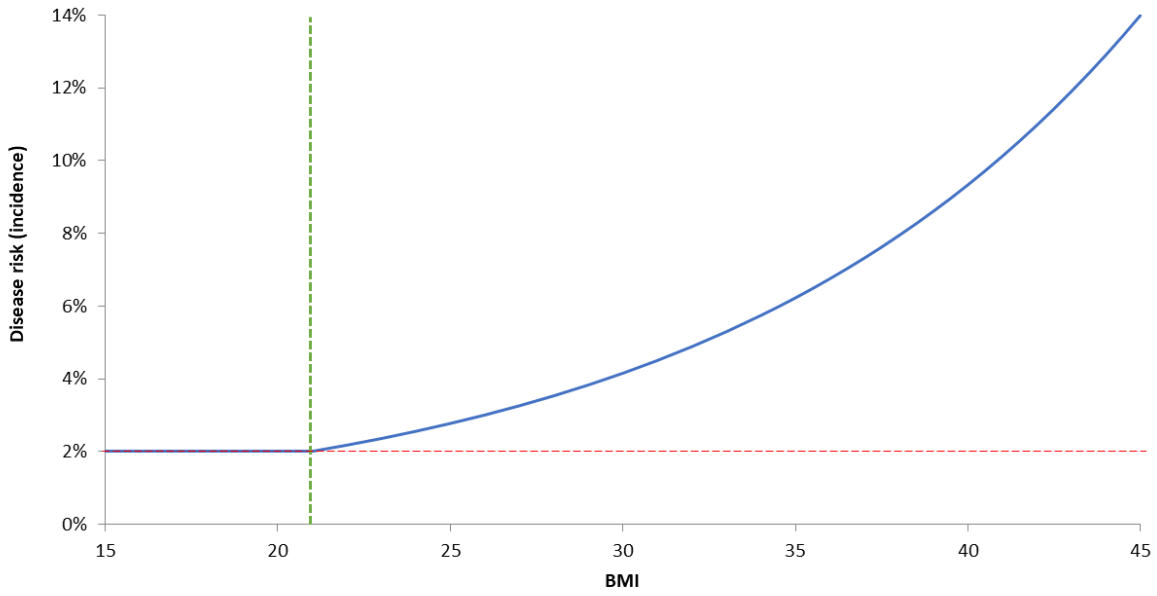
All the relative risk were calculated for every 5-unit change in BMI, i.e. a relative risk of 2 means that the risk would double if BMI increases by 5 kg/m^2. Whenever possible, different relative risks were applied to men and women separately and to different age groups.

HE2.4.262 Theoretical minimum risk and incidence

The theoretical minimum risk (TMR) is the BMI level associated with the lowest disease burden at the population level[3], i.e. the lowest risk of experiencing any disease. In the PRIMEtime model, the TMR was set at 21 kg/m^2 for all diseases included in the model. This was estimated by a WHO study that summarised the death and disability that was attributable to BMI around the world[3]. Although previous literature used other TMR values, for instance the International Agency for Research on Cancer (IARC) set TMR at 22 kg/m^2, the committee agreed to maintain the original value of 21, as they believed that any increase in BMI from 21 could affect the risk of developing a disease.

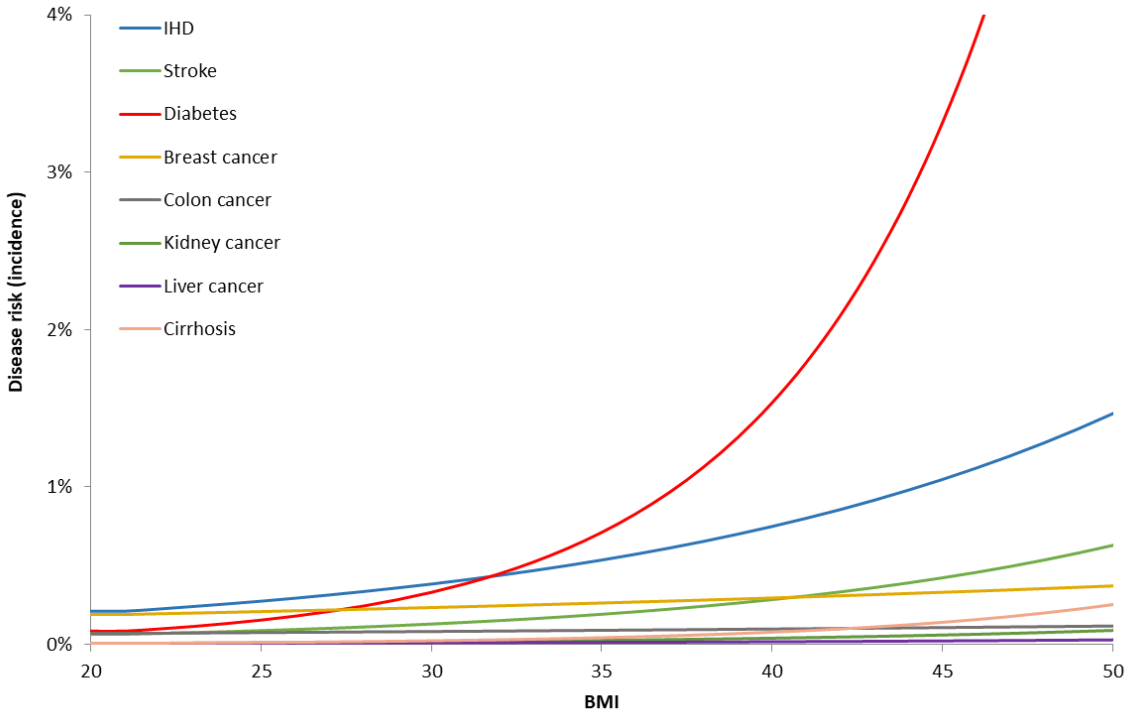
Once the TMR was agreed, the risk of disease at higher level of BMI was estimated by multiplying the relative risks in Table 7 by the difference between current BMI and the TMR. For instance, the risk of developing diabetes for a person with a BMI at 26 kg/m^2, 5 units above the TMR, is 2.16 higher than a person whose BMI equal to 21 (recall that the relative risks in Table 7 are calculated for every 5-unit increase in BMI). For BMI values lower than the TMR, it is assumed that the risk would not change as shown in Figure 6.

Figure 6: Theoretical minimum risk



Take a 60-year-old woman as an example, her risk of getting the diseases included in the model can be calculated based on the relative risks from Table 7 (see Figure 7). Diabetes and IHD both showed a steeper increase at high levels of BMI, which was caused by either high baseline rates (for IHD) or a high relative risk (for diabetes). The model predicts that a person with BMI at 35 kg/m^2 has a risk of developing diabetes 7.4 times higher than someone with a normal weight, and the risk reduces to 2.5 times higher for a person whose BMI at 25 kg/m^2. This is in line with a report from the Public Health England (PHE)[10] that found the risk of developing diabetes is 7 times higher for people living with obesity and threefold for overweight people. Regarding ischemic heart disease, the model predicts a 2.4 times greater risk for women with obesity compared with women with normal weight. This is also in line with published literature that reports a hazard ratio between 2 and 2.5[17]. This demonstrates that the model performs quite well when predicting the risk of a disease in people who are living with overweight or obesity, which is arguably an essential requirement for a disease-based model as PRIMEtime.

Figure 7: Relationship between BMI and modelled diseases (60-year-old woman)



HE2.4.233 Incidence calculation

As mentioned in section HE2.1, the population of the model is assigned to eleven BMI categories (see Table 8 and Figure 5). The effect of BMI on incidence of diseases (fourth column) is calculated as the difference between the TMR and the median BMI for each category divided by five (recall that the relative risk in Table 7 is defined for every 5-unit change in BMI). For the two BMI categories below the TMR, <15 and 15 to 20, it is assumed that there is no effect of BMI on the risk of developing any disease included in the model.

Table 8: BMI categories and effect (50 years old male)

BMI category	Midpoint BMI	Density	BMI effect[(a)]
<15	12.5	0%	0
15 to <20	17.5	1%	0
20 to <25	22.5	21%	0.3
25 to <30	27.5	45%	1.3
30 to <35	32.5	26%	2.3
35 to <40	37.5	6%	3.3
40 to <45	42.5	1%	4.3
45 to <50	47.5	0%	5.3
50 to <55	52.5	0%	6.3
55 to <60	57.5	0%	7.3
60+	62.5	0%	8.3

a) Calculated as (midpoint BMI – TMR) / 5

The disease incidence for each BMI category n (I_n) can be calculated with the following equation:

$$I_n = I_o \times RR^{e_n}$$

where I_o is baseline incidence when BMI is equal or lower than the TMR, RR is the disease-specific relative risk and e is the BMI effect defined in Table 9.

The baseline incidence I_o can be easily calculated using general population incidence and population density in each group through the following equation:

$$I_0 = \frac{I_{General\ population}}{\sum(D_n \times RR^{e_n})}$$

where $I_{General\ population}$ is the incidence of a particular disease in the general population estimated from the GBD, D_n is the population density (column 3 in Table 9) in the BMI category n, RR is the disease-specific relative risk and e_n is the BMI effect in BMI group n.

With I_o known, it allowed us to calculate the incidence of any disease for each BMI category I_n. These were then used to calculate the average disease incidence for the populations living with overweight or obesity based on the relevant BMI categories, e.g. for people with obesity, the last 7 categories with BMI above 30 were used for the calculation.

When a group of people receive a weight management intervention and achieve weight losses, they do not move to a different BMI category. Instead, their original midpoint BMI is reduced according to the treatment effect and used to estimate a lower incidence of diseases. Therefore, the model estimates the continuous and gradual effect of weight reduction on the risk of developing diseases instead of abrupt changes occurring when moving between discrete weight categories.

HE2.4.3 Effects of a low-energy total diet replacement intervention

The relative treatment effects of diet interventions were obtained from a systematic review of clinical studies (see HE1.1). The systematic reviews stratified the interventions based on the population enrolled in the trial. A meta-analysis was conducted for people with diabetes including trials enrolling only people with the disease (DIRECT and DIADEM-I) and a subgroup of people with diabetes from the DROPLET trial. Only the DROPLET trial was identified for the mixed population and no meta-analysis could be done for this group.

In line with the clinical review, the economic analysis stratified the population in two groups distinguishing a mixed population representative of the average person living with obesity or overweight in England and a population with diabetes. For the clinical effectiveness of the intervention, we used DROPLET trial for the mixed population and a meta-analysis using fixed effects model for people with diabetes. In both cases, different scenarios were explored to see if differences in cost-effectiveness arise if, for instance, the intervention was offered to people with a BMI higher than 25kg/m^2 instead of 30kg/m^2. A different cost for the intervention was used for people with diabetes and the mixed population using costs estimated from, respectively, DIRECT[30] and DROPLET[18] trials (see **Error! Reference source not found.**0).

In the following section, the methodologies used to estimate weight loss and weight regain are illustrated.

HE2.4.3.1 Weight loss

Weight loss was one of the main outcomes of all trials included in this analysis: DIRECT[19], DROPLET[4] and DIADEM-I[28].

The analysis on the mixed population used DRPLET data on weight loss at year 1 and 3, -7.60 kg and -3.60 kg respectively (Figure 8 and Figure 9). For the year in between, the mean value between these 2 was used assuming a constant rate of weight regain between year 1 and year 3. Beyond year 3 two different scenarios for regain were tested (see HE2.4.3.2).

Figure 8: Weight loss (kg) at 1 year – mixed population

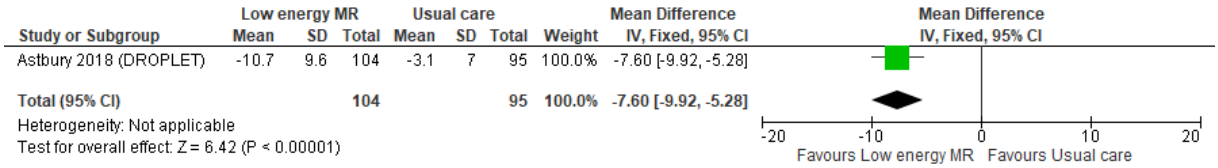
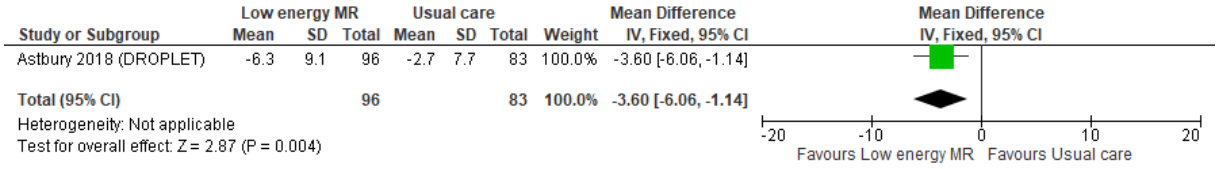


Figure 9: Weight loss (kg) at 3 years – mixed population



For people with diabetes, data were available for the first year in DIRECT, DIADEM-I and the subgroup of people in DROPLET with diabetes (see Figure 10). For year 2, data from the DIRECT trial were the only available (see Figure 11Figure 10).

Figure 10: Weight loss (kg) at 1 year – people with diabetes

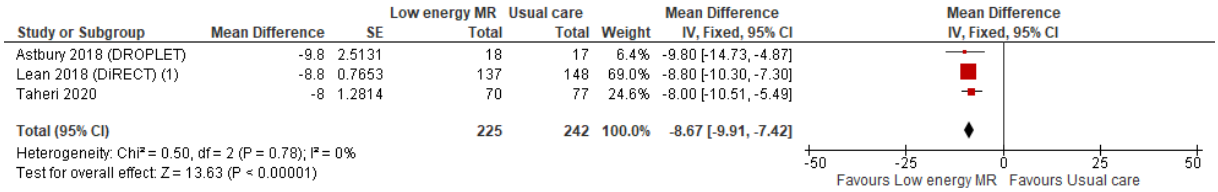
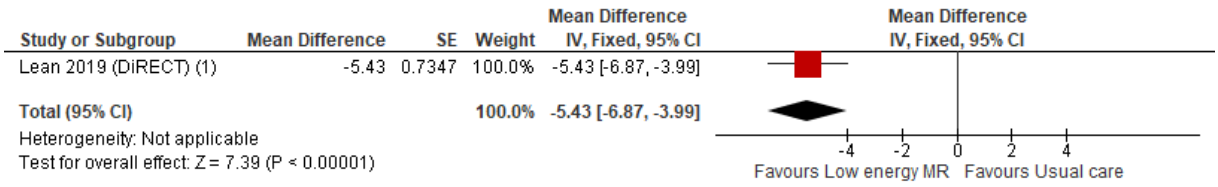


Figure 11: Weight loss (kg) at 2 years – people with diabetes



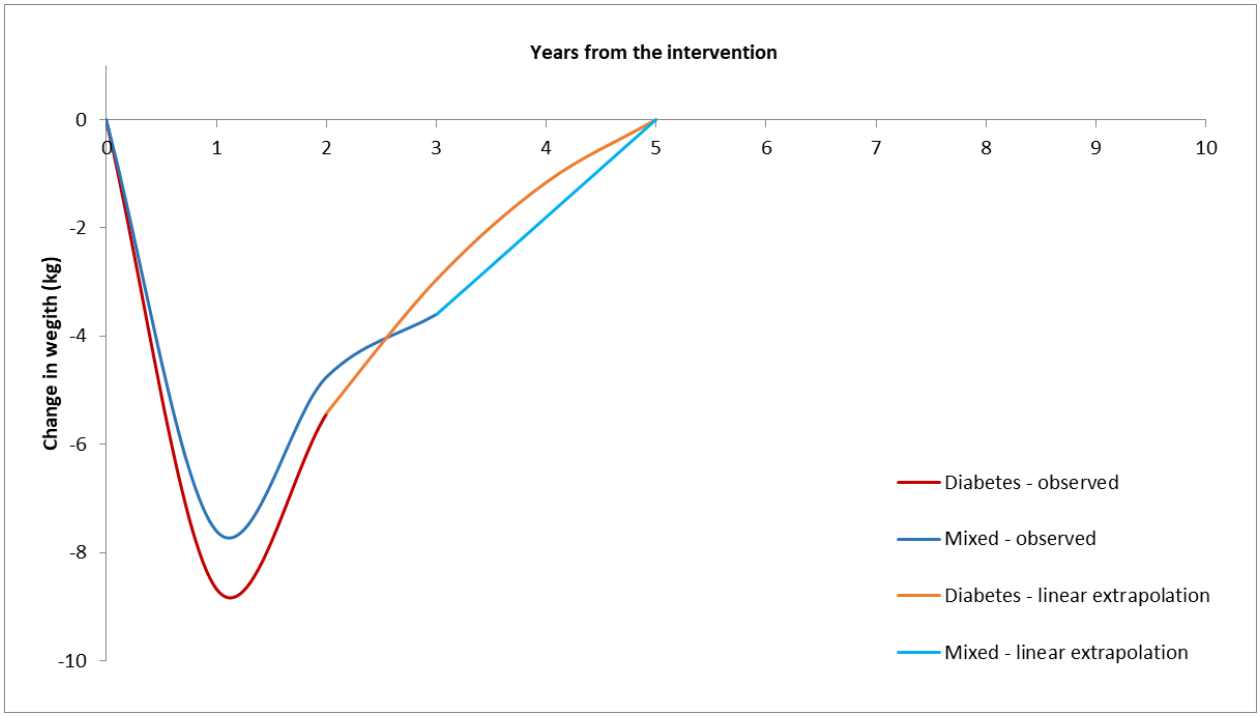
3-years data from the subgroup of DROPLET with diabetes were also available for the third year, but the sample size of 17 people was considered too small for this evidence to be used alone. Therefore, in people with diabetes, the extrapolated curve was used starting from year 3 instead of year 4 (see in HE2.4.3.2).

In both DROPLET and DIRECT trials, those with two or more follow-ups, weight loss was the largest in the first year but gradually decreased over time. Weight regain is a common feature of many weight management interventions and previous health economics analyses often relied on assumptions or expert opinion[5]. Next section (HE2.4.3.2) illustrates the methodology and assumptions used to estimate weight regain beyond the end of the trials.

HE2.4.312 Regain beyond last follow-up

The last follow-up available for the mixed population was 3 years (DROPLET[4]) and 2 for the population with diabetes (DIRECT[19]). Beyond these two data points weight regain is uncertain and needs to be extrapolated. Previous studies and systematic reviews[5] often relied on a linear regain trajectory with weight going back to the pre-intervention level in about 5 years. Figure 12 illustrates the long-term weight regain under this assumption, with the blue and the red curve representing observed data in, respectively, the population with diabetes and the mixed population, and the orange and light blue curves representing the linear extrapolation in the corresponding population.

Figure 12: Linear weight regain reaching pre-intervention level at year 5



Although this assumption is common in many economic evaluations with insufficient data points[18], it might not be appropriate for low-energy TDR interventions analysed in light of the evidence available. Firstly, all trials included in this analysis had supporting measures to ensure weight loss maintenance in the long-term. DiRECT[19], for instance, offered monthly short appointments with dietician or practice nurses and a rescue plan with partial or total meals replacement for those showing a great weight regain (>2kg or >4kg). Secondly, confidential 5 years data obtained from the principal investigators of the DIRECT trial seem to show a very different trend, with many people having a significantly lower weight 5 years after the intervention compared to the baseline.

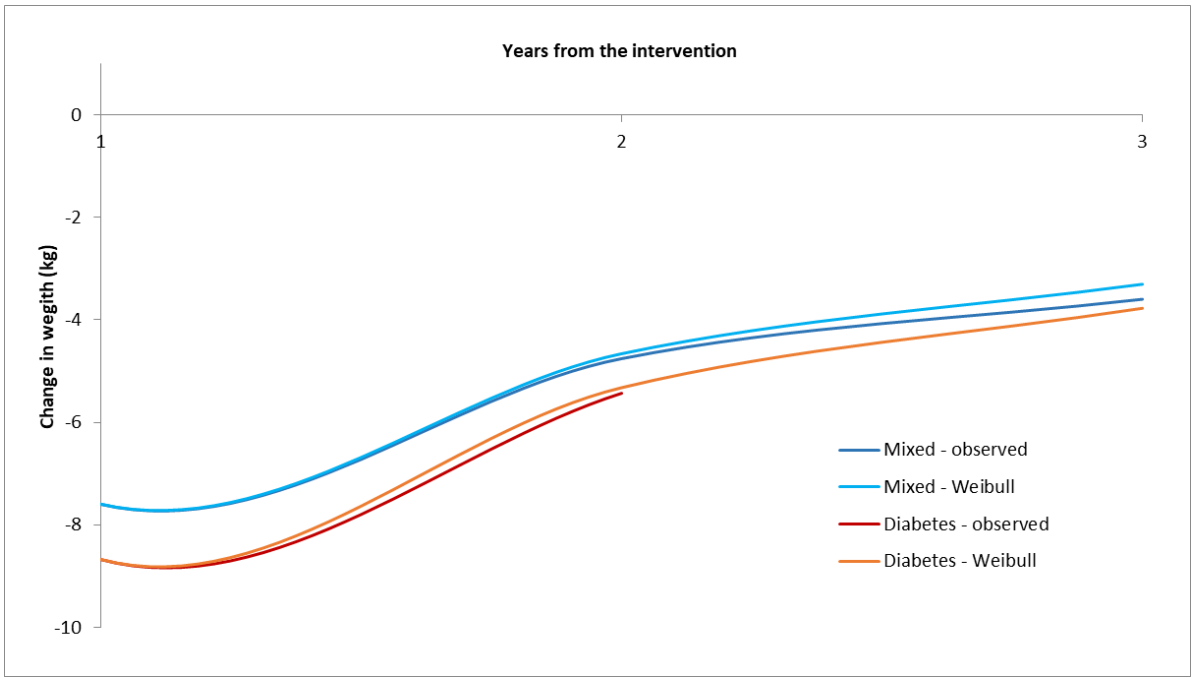
The 5 years from DIRECT suggested a non-linear reduction of clinical effectiveness, so more complex distributions that are able to incorporate a decreasing trend of reduction were explored. A very good candidate was the Weibull distribution. This is a continuous probability distribution extensively used in health care, economics, biology and engineering sciences and generally considered appropriate to model phenomena with increasing or decreasing trends. A two-parameter Weibull distribution was used defined by the following reliability function:

$$F(x) = \exp\left(-\left(\frac{x}{\alpha}\right)^{\gamma}\right)$$

where $F(x)$ is the weight regain expressed as a percentage of total initial weight loss, x is the time since the end of the intervention (year 1), and α and γ are, respectively, the scale and

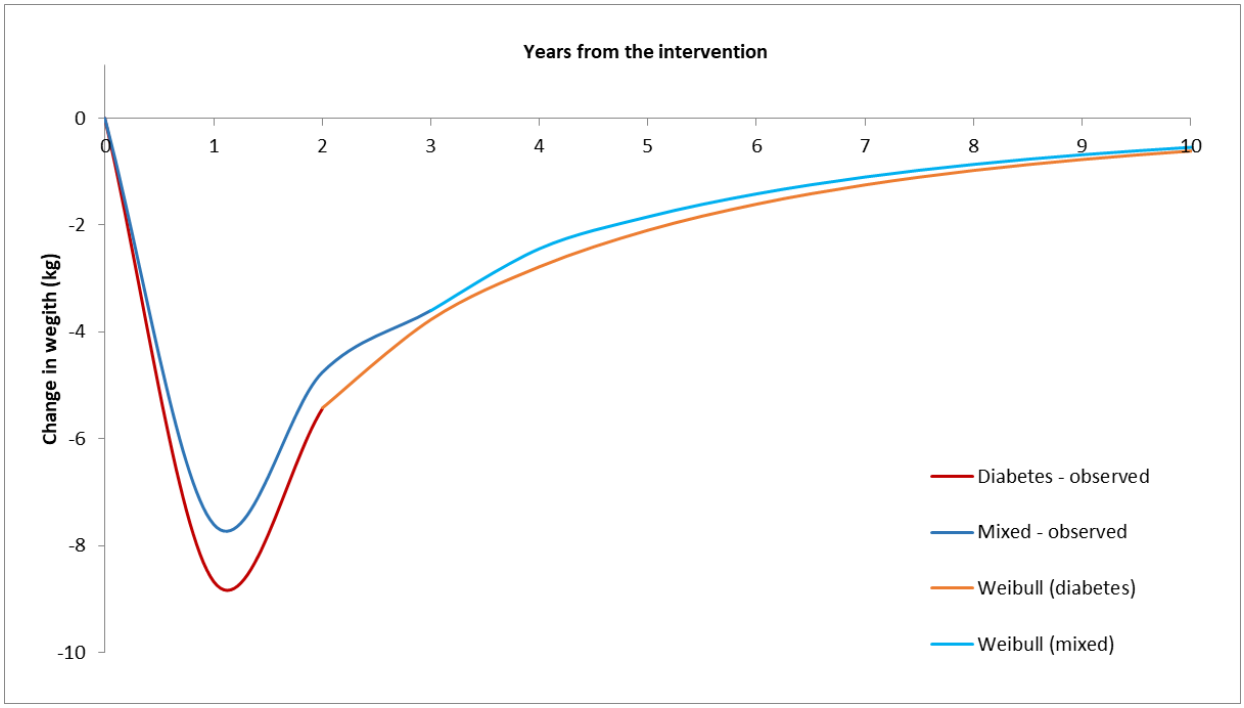
the shape parameters of the Weibull distribution. If γ is larger than 1, weight regain would grow exponentially with time, whereas if γ is below 1, the rate of weight regain would decrease. As the confidential data from DIRECT showed a decreasing trend, we set the shape parameter below 1. The extrapolation analysis was done with R studio using the package "rriskdistribution" and a Weibull curve was fitted to published and confidential data from DIRECT. Weight regain $F(x)$ was estimated as a percentage of regain on total initial weight loss. The estimated parameters of the Weibull curve were the following: α = 2.54 and γ = 0.77. Observed and predicted weight regain between years 1 and 2 are compared in Figure 13.

Figure 13: Observed and predicted weight regain between year 1 and year 3



Overall, weight regain predicted by the Weibull function is in line with observed weight regain from the trials and both share a similar shape and downward trend for weight regain. However, this extrapolation should be interpreted with caution as it was based only on few confidential data points and, therefore, both scenarios with the linear and the Weibull extrapolation were presented to the committee. The long-term trend in weight regain predicted using a Weibull distribution for both populations of interest is illustrated in Figure 14. The curve predicts a weight loss of around 2 kg at year 5 with the treatment effect eventually disappearing by year 10.

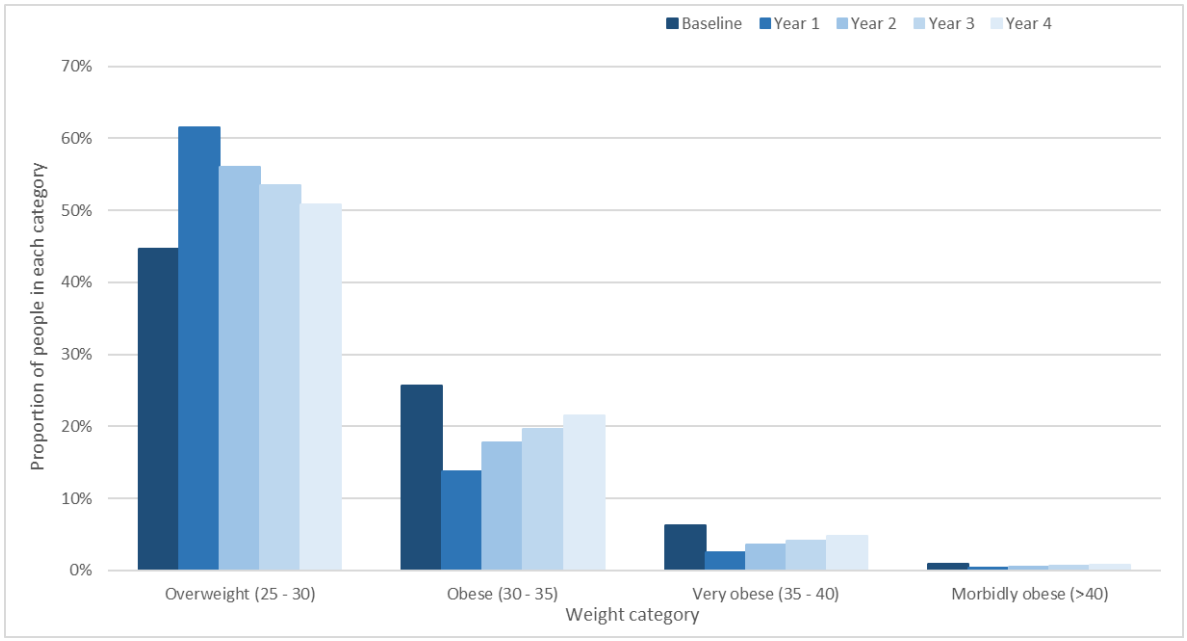
Figure 14: Observed and predicted weight regain over a period of 10 years



As stated before, two scenarios were presented using the Weibull and the linear distribution to extrapolate weight regain beyond the last observable data point. The latter scenario allows for an easier comparison with published health economic analyses that used linear regain[18].

Once weight loss and weight regain are estimated, a new BMI distribution for any year after the intervention can be calculated. As shown in Figure 15, the distribution significantly changes at year 1, with more people shifting to left to the overweight category, but then gradually goes back over the years to the baseline starting point.

Figure 15: BMI distribution after a TDR intervention for people living with obesity (50 years old males with BMI >30 kg/m ^{2})



The new BMI distribution allowed us to calculate new disease incidence and prevalence in the group who received the intervention through the methodology described in section

HE2.4.2. The new prevalence of the diseases was then used to estimate difference in QALYs and healthcare costs between the intervention and control group.

HE2.4.33 Remission from diabetes

The DIRECT trial reported as one of the main outcomes the proportion of people achieving remission from diabetes. The study recruited 289 adults with a diagnosis of diabetes and observed how many people were in remission at year 1 and 2. They found a much higher remission rate in the intervention group compared to the control group (Table 9).

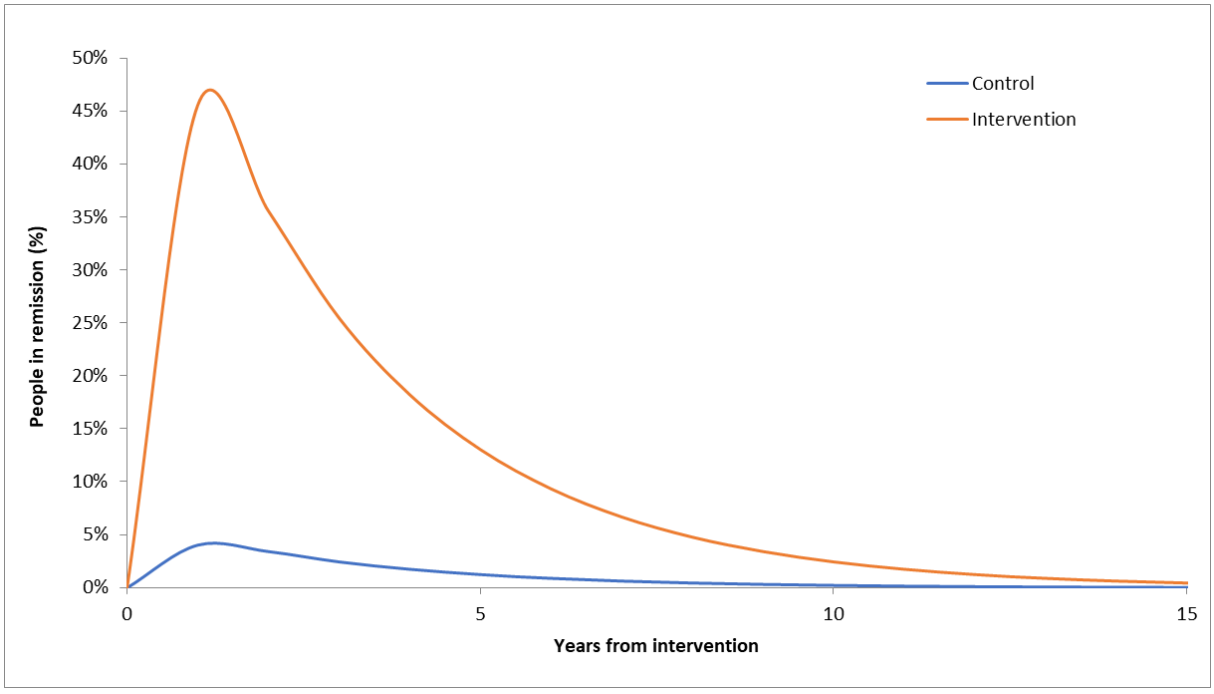
Table 9: Remission from diabetes in DiRECT trial

Disease	Intervention (%)	Control (%)	Source
Remission – year 1	45.6 (37.6 to 53)	4.0 (1.3 to 7.4)	DiRECT[19], Xin 2020[30]
Remission – year 2	35.6 (28.2 to 43.0)	3.4 (0.7 to 6.7)	DiRECT[19], Xin 2020[30]
Relapse rate – year 2[(a)]	28.4 (18.7 to 38.6)		DiRECT[19], Xin 2020[30]

a) *The relapse rate was calculated by dividing the number of people in remission at first year who relapsed in the second year by the number of people who achieved remission in the first year*

To incorporate the effects of remission from diabetes into the model, the same methodology used by Xin 2020 was adopted[30]. For the first two annual cycles after the intervention, we assigned the proportions from Table 9 to the intervention and control groups using a partitioned survival model. For cycles beyond the second, the proportions of people remaining in remission in both arms were estimated using the relapse rate observed in year 2. Figure 16 shows the percentage of people with diabetes in remission after the intervention.

Figure 16: Remission over time in the remission and control group



The assumption behind this approach is that the relapse rate observed between year 1 and year 2 would remain constant over years, which may not necessarily be the case. If relapse rate increases with time, it is possible that the model is overestimating the number of people in remission at every cycle. However, as recent literature suggest that BMI and diabetes status are highly correlated[13], the relapse rate may be similar to BMI weight regain. As data from DIRECT showed a decreasing trend in weight regain (see HE2.4.3.2), it is possible that

the relapse rate would behave similarly and, therefore, the constant assumption may instead underestimate the number years people live in remission.

While in remission, people have the same quality of life and mortality as the general population. It is also assumed they would not incur any healthcare cost, although it is likely they would still be monitored while they are in remission to ensure their blood sugar levels remain below the critical range for diabetes. Remission from diabetes was included in the analysis on the population of people diabetes which reflects closely the participants of DIRECT and DIADEM-I trial. The original PRIMEtime model did not include remission from any disease, and the same assumption was kept in the analysis on mixed population to allow comparison with similar published analysis that used PRIMEtime. As it is possible to achieve remission from other diseases included in the model, it might be that the model is overestimating the length and impact of such diseases and, consequently, the benefits of the intervention. Likewise, the model is unable to capture any improvement in disease severity caused by a reduction of the person's BMI, which may underestimate the cost-effectiveness of the intervention.

HE2.4.4 Resource use and costs

HE2.4.4.1 Diet intervention costs

The costs of low-energy TDR interventions were collected from two costs analyses available in the literature[18, 30]. For the intervention targeting the mixed population, the cost estimated for the TDR in DROPLET trial was utilized (see Table 10).

Table 10: Cost of DROPLET intervention (1 year) – per person

Component	Quantity	Unit cost	Total cost
GP attendance	4 minutes	£4.14 per minute	£16.49
GP medication review	2 for 30% of people	£37.82 per review	£22.69
Meal replacement products	315 single meals	£2.40[(a)]	£756.88
Total			£796.04

Source: Kent 2019[18]

a) Priced to incorporate the cost of the behavioural support

From the total cost of £796, the estimated cost of standard practice (nurse-led behavioural support programme including 2 minutes for GP referral and 4 attendances with a nurse practitioner) equal to £34,06 was subtracted to calculate the incremental cost of offering the programme: £762. This value was inflated to 2020-2021 prices (£811) using the NHS cost inflation index (NHSCII)[16].

The cost of a TDR offered to people with diabetes was estimated using the cost-analysis reported in the DIRECT trial[30] (see Table 11) as this trial enrolled exclusively people with diabetes and made achieving high rate of remission one of the main outcome of the study.

Table 11: Cost of DIRECT intervention (2 years) – per person

Component	Quantity	Unit cost	Total cost
Set-up cost	1	£45	£45
Sachets issued	590	£1.42	£838
Practice nurse or dietitian visits	23 (25 – 35 min/appointment)	£42 per hour	£506
Counterweight-plus booklets	1	£20	£20
Total (1 year)			£1137

Component	Quantity	Unit cost	Total cost
Total over 2 years [a]			£1411

Source: Xin 2020[30]

a) Year 2 cost discounted using an annual rate of 3.5%

The final cost of £1,411 was inflated to 2020-2021 prices (£1,477) using using the NHS cost inflation index (NHSCII)[16].

The cost estimated for DIRECT is significantly higher than DROPLET reflecting the higher number of visits of nurses and dietitians required to follow-up people with type 2 diabetes and the additional support to avoid cases of diabetes relapses over the two years of the intervention. Therefore, we used the cost identified in DROPLET in the scenario where the intervention is given to a mixed population, and the cost from DIRECT in the scenario where the intervention is offered to those with a recent diagnosis of type 2 diabetes.

HE2.4.11 Health states costs

Costs associated with all diseases except cirrhosis were taken from a recent study that used PRIMEtime to evaluate three current obesity intervention policies[8]. The cost of cirrhosis was not available from the same source and therefore a less recent study[6] using the same methodology was used instead with the cost being inflated to 2020-2021. Costs were calculated from aggregate budgets using a top-down approach: total costs from NHS programme budgeting data were divided by the prevalence or incidence collected from the Hospital Episode Statistics (HES) to calculate the cost per prevalent or incident case. Table 12 illustrates the costs used in the model.

Table 12: Health states costs

Disease	Unit cost	Confidence intervals 95%	Source
IHD	£606 per prevalent case	369 – 844	Cobiac 2022[8]
Stroke	£1,950 per prevalent case	1,186 – 2,714	Cobiac 2022[8]
Diabetes	£187 per prevalent case	113 – 260	Cobiac 2022[8]
Breast cancer	£12,433 per incident case	7,559 – 17,306	Cobiac 2022[8]
Colorectal cancer	£9,204 per incident case	5,596 – 12,812	Cobiac 2022[8]
Liver cancer	£2,172 per incident case	1,320 – 3,023	Cobiac 2022[8]
Kidney cancer	£4,979 per incident case	3,027 – 6,931	Cobiac 2022[8]
Cirrhosis	£342 per prevalent case	1,639 – 3,752	Briggs 2018 inflated to 2020-2021[6]

Diseases that are expected to cause a continuous and persistent cost, such as diabetes or IHD, were costed using their prevalent case numbers and their costs were accrued throughout the model at each cycle. Diseases that are associated with a very high first year cost and lower costs thereafter, such as cancer, were costed used their incident cases with the assumption that most of their costs would occur during the first year after the diagnosis.

HE2.4.413 Social care costs

Formal social care costs in the original PRIMEtime model were estimated using the tool develop by the Department of Health[7]. The tool estimates the age- and gender-specific probability and amount of social care received following a change in quality of life, which is quantified using EuroQol five dimensions questionnaire (EQ-5D, see HE2.4.5). The tool includes social care (defined as formal care), informal care (provided by family and friends), private paid, private unpaid and government (services provided by the government and not included in other categories). As the committee were aware that social costs associated with many obesity-related diseases are significant, the tool results were included in this analysis but limited to social or formal care only, that is the one provided by paid health and social care staff in care homes, hospitals and at home. The model assumes that people would start requiring social care from the age 75 onward.

Some limitations have previously been raised regarding the methodology used by Department of Health to estimate social care costs[6]. The most important is the use of change in quality of life as a key driver of social care costs irrespective of diagnosis or on other individual characteristics as BMI. This may underestimate the effect of certain diagnosis on people's self-care beyond their EQ-5D scores. Moreover, obesity is known to be associated with several musculoskeletal disorders[29] that can severely hinder mobility and could require paid social care. This would not be captured as the model does not allow for BMI and weight status to influence quality of life beyond the mechanism of the diseases includes (see section HE3.3.3).

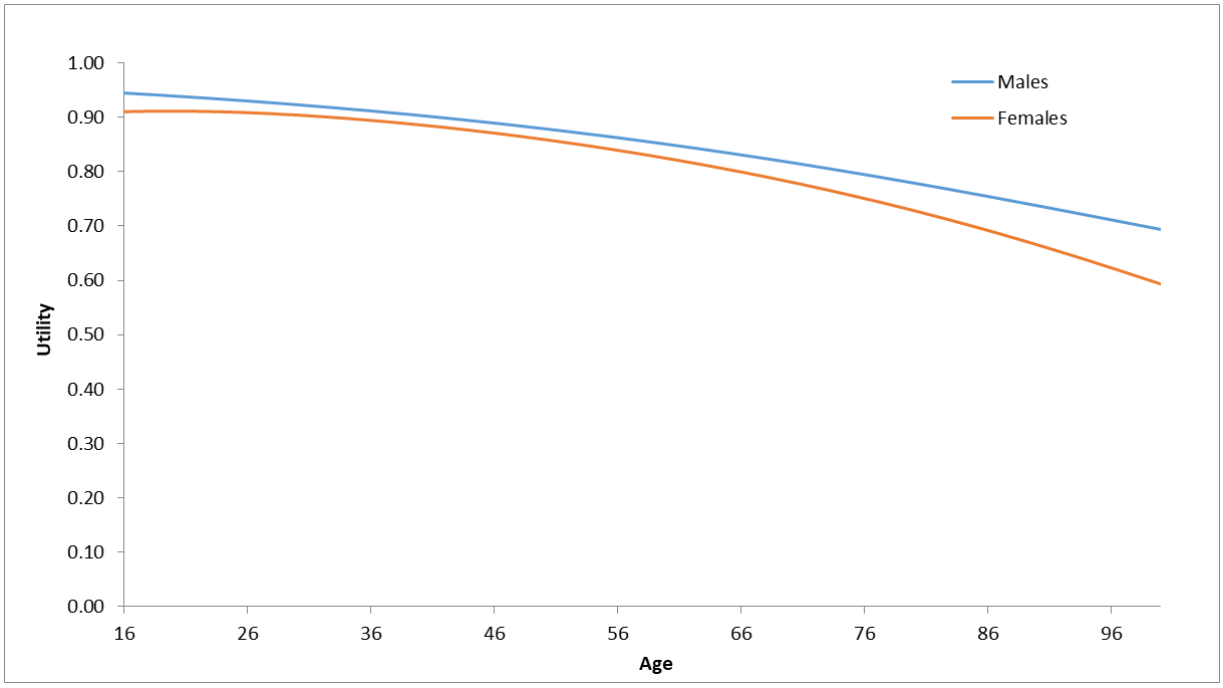
HE2.4.425 Quality of life

HE2.4.5.231 General population

As direct interaction between body weight (status) and quality of life is not allowed in PRIMEtime to avoid double counting, people with no disease share the same quality of life of the general population regardless of their BMI.

EQ-5D 3L utility scores in the general population was estimated using the Adjusted Limited Dependent Variable Mixture Models (ALDVMM) developed by Hernández Alava and colleagues[14] and based on the Health Survey for England 2014. The model was developed in 2022 by the Decision Support Unit (DSU) of NICE and it is expected to reflect more realistically quality of life of English population (see Figure 17)

Figure 17: EQ-5D in the general population by gender



Source: Hernández Alava[14]

HE2.4.5.142 Disease QoL

EQ-5D utility scores of people with a modelled diseases were based on the Catalogue of EQ-5D scores for the United Kingdom developed by Sullivan and colleagues[27]. These are reported in Table 13 below.

Table 13: Losses of utilities associated with incident and prevalence cases of all diseases

Disease	Incidence / prevalence	Mean reduction	Standard deviation
IHD	Incidence	-0.063	0.025
	Prevalence	-0.037	0.015
Stroke	Incidence	-0.117	0.019
	Prevalence	-0.073	0.031
Diabetes	Prevalence	-0.071	0.005
Breast cancer	Prevalence	-0.019	0.014
Colorectal cancer	Prevalence	-0.067	0.017
Liver cancer	Prevalence	-0.093	0.044
Kidney cancer	Prevalence	-0.048	0.041
Pancreas cancer	Prevalence	-0.086	0.027
Cirrhosis	Prevalence	-0.083	0.031

Source: Sullivan 2011[27]

Incidence utility reductions were applied to people developing the disease at each cycle and reflect the decline in quality of life associated with the acute phase of the disease during its onset. Prevalence utility reductions were applied to all people with the prevalence condition at each cycle (i.e. those with the disease). These decrements quantify the long-term sustained reduction in quality of life associated with the specific health condition.

IHD and stroke affect utilities both through their incidence and prevalence at each year. This was done to account for the higher harm caused by the disease during its acute phase, which lasts for one annual cycle, followed by the milder impact of its chronic phase that lasts over the lifetime of the person. When IHD or stroke occur in a certain cycle, only their incidence QALY detriment is applied to avoid double counting. All the other diseases affect quality of life through their prevalence and are therefore considered chronic in the PRIMEtime model.

HE2.486 Summary

All parameters used in the model are summarised in Table 14, including details of the distributions and parameters used in probabilistic analysis.

Table 14: All parameters in original cost–utility model

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
General settings				
Time horizon	Lifetime	n/a	n/a	NICE reference case
Discount rates	3.5%	n/a	n/a	NICE reference case
Cycle length	12 months	n/a	n/a	Assumed
Cohort settings				
Starting age	50	n/a	n/a	HSE 2017-2019[15]
Proportion of females	54%	n/a	n/a	ONS 2020[1]
Average BMI in males by age	50 – 54 = 28.4 55 – 59 = 29.1 60 – 64 = 28.7 65 – 69 = 29.3 70 – 74 = 29.2 75 – 80 = 29.2 80 – 85 = 27.4 85 – 89 = 26.3 >90 = 26	Lognormal	μ', σ' = 3.33, 0.15 μ', σ' = 3.36, 0.18 μ', σ' = 3.34, 0.16 μ', σ' = 3.36, 0.18 μ', σ' = 3.36, 0.16 μ', σ' = 3.33, 0.15 μ', σ' = 3.30, 0.13 μ', σ' = 3.26, 0.13 μ', σ' = 3.25, 0.08	HSE 2019[15]
Average BMI in females by age	50 – 54 = 28.7 55 – 59 = 28.3 60 – 64 = 28.3 65 – 69 = 28.1 70 – 74 = 28.1 75 – 80 = 28.1 80 – 85 = 27.4 85 – 89 = 27 >90 = 27	Lognormal	μ', σ' = 3.33, 0.23 μ', σ' = 3.32, 0.21 μ', σ' = 3.32, 0.22 μ', σ' = 3.31, 0.21 μ', σ' = 3.32, 0.2 μ', σ' = 3.31, 0.20 μ', σ' = 3.29, 0.19 μ', σ' = 3.28, 0.17 μ', σ' = 3.28, 0.17	HSE 2019[15]
Mean height	Males: 175 cm Females: 163 cm	n/a	n/a	HSE 2017 – 2019[15]
Mortality in the general population	Gender- and age- specific	n/a	n/a	ONS life tables 2017-2019[1]

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Baseline diseases characteristics				
Age- and disease-specific incidence	Gender- and age- specific using Disbayes package for R studio	n/a	n/a	Global Burden of Disease (GBD) [21]
Age- and disease-specific case fatality	Gender- and age- specific using Disbayes package for R studio	n/a	n/a	Global Burden of Disease (GBD) [21]
Age- and disease-specific prevalence	Gender- and age- specific using Disbayes package for R studio	n/a	n/a	Global Burden of Disease (GBD) [21]
Diabetes – incidence rate ratio by weight status, males	BMI > 25 = 1.95 BMI > 30 = 2.23	Lognormal	μ', σ' = 0.66, 0.1 μ', σ' = 0.8, 0.07	HSE 2017 – 2019[15]
Diabetes – incidence rate ratio by weight status, females	BMI > 25 = 3.36 BMI > 30 = 2.61	Lognormal	μ', σ' = 1.21, 0.12 μ', σ' = 0.96, 0.07	HSE 2017 – 2019[15]
IHD – incidence rate ratio by weight status, males	BMI > 25 = 1.40 BMI > 30 = 1.44	Lognormal	μ', σ' = 0.32, 0.18 μ', σ' = 0.36, 0.14	HSE 2017 – 2019[15]
IHD – incidence rate ratio by weight status, females	BMI > 25 = 1.88 BMI > 30 = 1.32	Lognormal	μ', σ' = 0.6, 0.24 μ', σ' = 0.26, 0.19	HSE 2017 – 2019[15]
Stroke – incidence rate ratio by weight status, males	BMI > 25 = 1.07 BMI > 30 = 1.44	Lognormal	μ', σ' = 0.04, 0.25 μ', σ' = 0.41, 0.21	HSE 2017 – 2019[15]
Stroke – incidence rate ratio by weight status, females	BMI > 25 = 1.01 BMI > 30 = 1.19	Lognormal	μ', σ' = -0.02, 0.25 μ', σ' = 0.14, 0.25	HSE 2017 – 2019[15]
Cirrhosis – incidence rate ratio by weight status, males	BMI > 25 = 2.06 BMI > 30 = 1.40	Lognormal	μ', σ' = 0.53, 0.62 μ', σ' = 0.24, 0.45	HSE 2017 – 2019[15]
Cirrhosis – incidence rate ratio by weight status, females	BMI > 25 = 1.72 BMI > 30 = 1.39	Lognormal	μ', σ' = 0.88, 0.39 μ', σ' = 0.21, 0.48	HSE 2017 – 2019[15]
Total diet replacement effectiveness				
Mixed population – weight loss (kgs)	1 year = 7.6 3 years = 3.6	Lognormal	μ', σ' = 2.02, 0.15 μ', σ' = 1.22, 0.34	DROPLET[4]

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
People with diabetes – weight loss (kgs)	1 year = 8.67 2 years = 5.43	Lognormal	μ', σ' = 2.16, 0.07 μ', σ' = 1.68, 0.13	DIRECT[19] DROPLET[4] DIADEM-I[28]
Weibull weight regain curve	α = 2.54 γ = 0.77	n.a.	n.a.	Extrapolated using DIRECT 5 years data
Relative risks (per 5 units increase of BMI)				
Diabetes	BMI < 25 = 0.96 BMI > 25 = 2.16	Lognormal	μ', σ' = -0.07, 0.25 μ', σ' = 0.771, 0.07	Prospective Study Collaboration[22]
IHD	By age: 35 – 59 = 1.5 60 – 69 = 1.4 70 – 79 = 1.31 80 – 89 = 1.3	Lognormal	μ', σ' = 0.4, 0.04 μ', σ' = 0.34, 0.03 μ', σ' = 0.27, 0.06 μ', σ' = 0.56, 0.07	Prospective Study Collaboration[22]
Stroke	By age: 35 – 59 = 1.76 60 – 69 = 1.49 70 – 79 = 1.33 80 – 89 = 1.10	Lognormal	μ', σ' = 0.56, 0.07 μ', σ' = 0.40, 0.06 μ', σ' = 0.28, 0.06 μ', σ' = 0.09, 0.08	Prospective Study Collaboration[22]
Cirrhosis	BMI < 25 = 0.73 BMI > 25 = 1.79	Lognormal	μ', σ' = -0.33, 0.16 μ', σ' = 0.58, 0.08	Prospective Study Collaboration[22]
Liver cancer	1.47	Lognormal	μ', σ' = 0.38, 0.08	Prospective Study Collaboration[22]
Breast cancer	Only women Age < 60 = 1 Age > 60 = 1.12	Lognormal	μ', σ' = 0.11, 0.02	Prospective Study Collaboration[22]
Colorectal cancer	Men = 1.24 Women = 1.09	Lognormal	μ', σ' = 0.21, 0.02 μ', σ' = 0.09, 0.02	Prospective Study Collaboration[22]
Kidney cancer	Men = 1.24 Women = 1.34	Lognormal	μ', σ' = 0.21, 0.04 μ', σ' = 0.29, 0.02	Prospective Study Collaboration[22]
Theoretical minimum risk	BMI = 21	n/a	n/a	Arnold 2015[3]
Remission from diabetes				
Intervention (TDR) – annual probability	Year 1 = 0.46 Years 2+ = 0.36	Beta	α, β = 68, 81 α, β = 53, 96	DIRECT[19]
Usual care (control) – annual probability	Year 1 = 0.04 Years 2+ = 0.03	Beta	α, β = 6, 143 α, β = 5, 144	DIRECT[19]
Relapse annual probability	Years 2+ = 0.28	Beta	α, β = 21, 53	DIRECT[19]
Costs				

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
DROPLET intervention	£811	n/a	n/a	Kent 2019[18] inflated to 2020-2021[16]
DIRECT intervention	£1,477	n/a	n/a	Xin 2020[30] inflated to 2020-2021[16]
IHD prevalent case	£606	Lognormal	μ', σ' = 5.96, 0.2	Cobiac 2022[8]
Stroke prevalent case	£1,950	Lognormal	μ', σ' = 7.13, 0.2	Cobiac 2022[8]
Diabetes prevalent case	£187	Lognormal	μ', σ' = 4.78, 0.2	Cobiac 2022[8]
Breast cancer incident case	£12,433	Lognormal	μ', σ' = 8.98, 0.2	Cobiac 2022[8]
Colorectal cancer incident case	£9,204	Lognormal	μ', σ' = 8.68, 0.2	Cobiac 2022[8]
Liver cancer incident case	£2,172	Lognormal	μ', σ' = 7.23, 0.2	Cobiac 2022[8]
Kidney cancer incident case	£4,979	Lognormal	μ', σ' = 7.23, 0.2	Cobiac 2022[8]
Pancreas cancer incident case	£2,695	Lognormal	μ', σ' = 7.45, 0.2	Cobiac 2022[8]
Cirrhosis prevalent case	£342	Lognormal	μ', σ' = 7.4, 0.2	Cobiac 2022[8]
Social care costs	Calculated through DHSC tool for each age and gender	n/a	n/a	Claxton 2015[7]
Inflation adjustment for social care costs	0.643	n/a	n/a	Health Index from Unit Costs of Health and Social Care 2018[9]
Utility				
General population	Gender- and age-specific	n/a	n/a	NICE DSU unit[14]
IHD incidence	-0.063	Normal	μ', σ' = -0.063, 0.02	Sullivan 2011[27]
IHD prevalence	-0.037	Normal	μ', σ' = -0.037, 0.01	Sullivan 2011[27]
Stroke incidence	-0.117	Normal	μ', σ' = -0.117, 0.02	Sullivan 2011[27]
Stroke prevalence	-0.073	Normal	μ', σ' = -0.073, 0.03	Sullivan 2011[27]
Diabetes	-0.071	Normal	μ', σ' = -0.071, 0.00	Sullivan 2011[27]
Breast cancer	-0.019	Normal	μ', σ' = -0.019, 0.01	Sullivan 2011[27]
Colorectal cancer	-0.067	Normal	μ', σ' = -0.067, 0.02	Sullivan 2011[27]
Liver cancer	-0.093	Normal	μ', σ' = -0.093, 0.04	Sullivan 2011[27]

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Kidney cancer	-0.048	Normal	μ', σ' = -0.048, 0.04	Sullivan 2011[27]
Pancreas cancer	-0.086	Normal	μ', σ' = -0.086, 0.03	Sullivan 2011[27]
Cirrhosis	-0.083	Normal	μ', σ' = -0.083, 0.03	Sullivan 2011[27]

HE2.5 Summary of key assumptions

The following main assumptions were made over the course of model development:

1. BMI affects people's health and NHS healthcare costs only thought the channel of BMI-related diseases. Direct impacts of a high BMI on health, for instance mental health or mobility, are not included.
2. All disease included in the models are chronic. This means they cause a healthcare cost, higher mortality and a loss in utility for the entire lifetime of the person. Different costs and quality of life are applied in the first cycles for some diseases when appropriate i.e. when the disease has a higher impact during its acute phase
3. Remission, i.e. transition from a disease to a healthy state, is allowed only for diabetes and only in the subgroup of people reflecting DIRECT population. This conclusion is drawn from the data obtained from the DIRECT study, which showed that the intervention increased the probability of diabetes remission among those who lost weight. All individuals who achieved remission are assumed to experience a relapse in the long term, as their weight returns to pre-intervention levels.

HE2.6 Subgroup analyses

The model was run for 4 different populations:

- People who are living with diabetes and overweight (BMI > 25)
- People who are living with diabetes and obesity (BMI > 30)
- Mixed population who are living with overweight (BMI > 25)
- Mixed population who are living with obesity (BMI > 30)

The results are reported separately for each population in section 0.

HE2.7 Sensitivity analyses

HE2.7.1 Deterministic sensitivity analyses

A range of deterministic analyses were made to test the robustness of the assumptions made in this analysis (see Table 6). The Committee identified weight regain as the most important assumption of the model as it significantly affects the final outcomes of the model. In the base case scenario, a Weibull distribution based on 4 years data from DIRECT was used but was considered optimistic by some members of the committee. Therefore, a more "conservative" assumption using a linear regain reaching 0 (full weight regain) at year 5 was tested in the scenario analysis. In a few published economic evaluations on public health interventions (Kent 2019), a discount rate of 1.5% was used instead of the higher reference case commonly used by NICE (3.5%). Therefore, we included a further scenario using a 1.5% discounting rate to allow comparison with similar analyses.

Table 15: Scenario analyses

Feature	Scenario	Description
Weight regain	Weibull curve*	Weight regain is simulated using the Weibull curve fitted on 4 years unpublished DIRECT data
	Linear regain	Weight is assumed to be fully regain in 5 years following a linear trend
Discount rates	3.5%*	Costs and health outcomes are discounted at 3.5%
	1.5%	Cost and health outcomes are discounted at 1.5%

** Base case assumption*

HE2.7.2 Probabilistic sensitivity analyses

The model was developed to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. We specified probability distributions for all input variables with the exception of the intervention costs, that were taken from the trials. We decided the type of distribution with reference to the properties of data of that type (for example, we use beta distributions for probabilities that are bounded between 0 and 1 and we use gamma distributions for cost parameters that cannot be negative). Where possible, we parameterised each distribution using dispersion data from the source from which the value was obtained; where no such data were available, we gave consideration to applying plausible ranges based on committee advice and the usual properties of similar data.

HE3 Results

HE3.1 Clinical outcomes

Changes in BMI distribution in the 4 years following the intervention are shown in **Figure 18** and **Figure 19** for, respectively, the Weibull and linear regain scenarios. In both scenarios, weight distribution tends to return to the baseline values due to the regain although the process is faster with a linear regain (**Figure 19**)

Figure 18: Proportion of people in each weight category (Weibull regain)

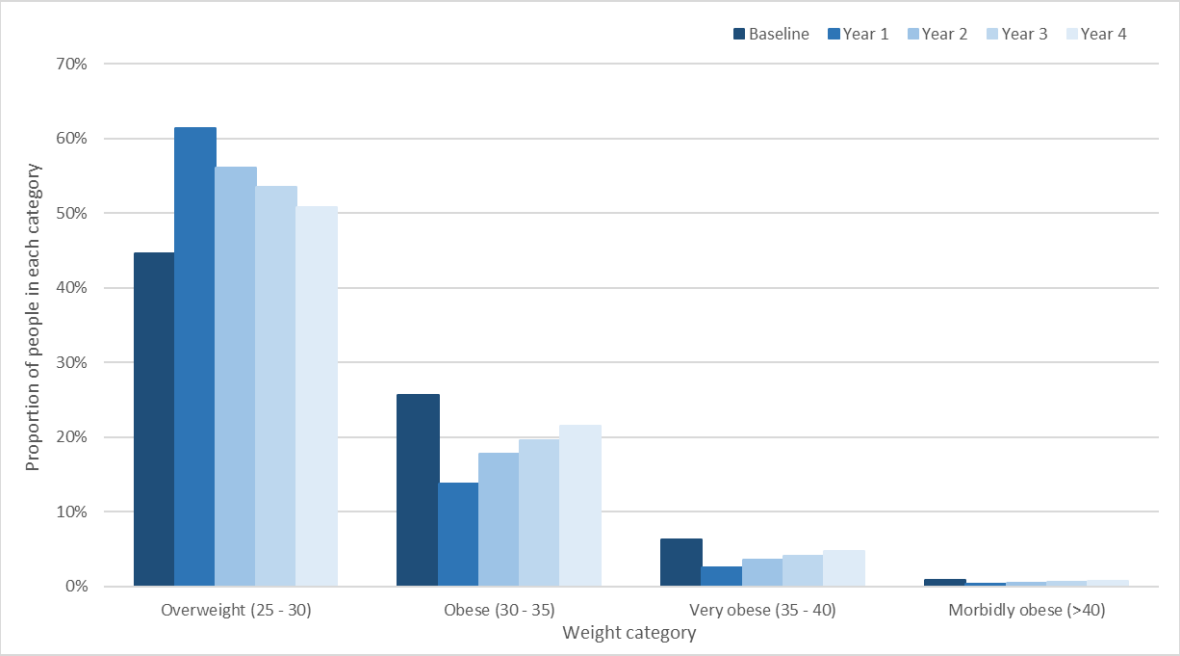
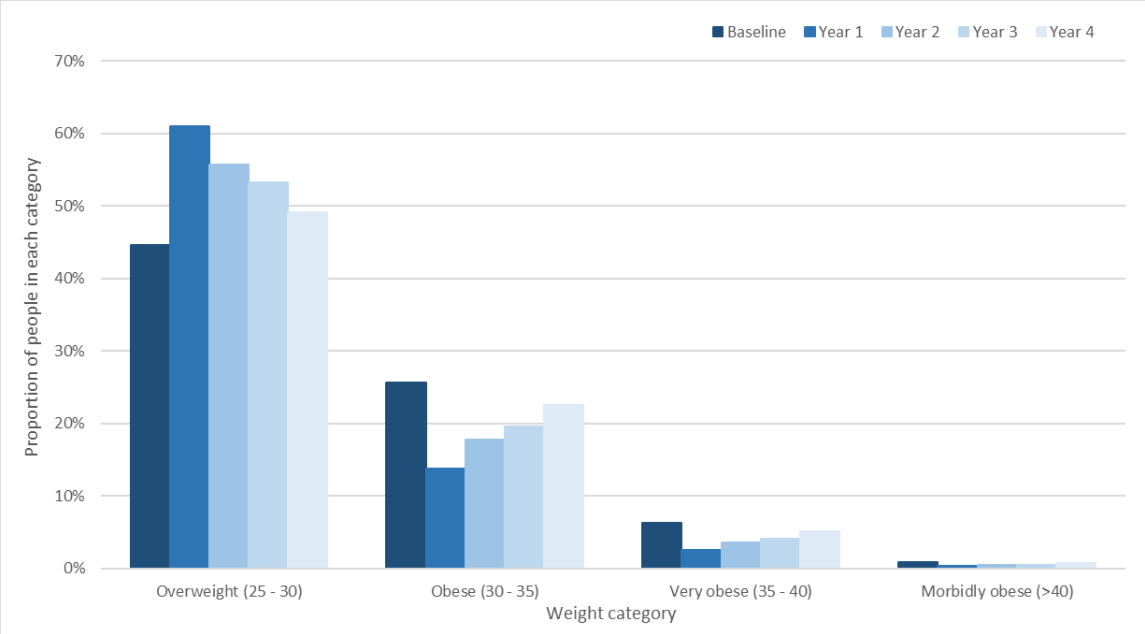


Figure 19: Proportion of people in each weight category (Linear regain)



Error! Reference source not found. shows the number of cases averted with a low-energy diet intervention in a mixed population who are living with obesity (BMI > 30). As diabetes was found to be strongly correlated with higher BMI levels, it is also the disease that experiences the most substantial prevention through the intervention. It is noteworthy that a significant number of cases of ischemic heart disease are prevented, particularly among men who have a higher lifetime risk of developing the disease.

It is important to highlight that the model predicts an increase in the number of cases of colorectal and liver cancer after the intervention. However, this is primarily attributed to the extended life expectancy associated with the intervention, which increases the number of people at risk of developing late-life disease, rather than a direct effect of the intervention on cancer development.

Table 16: Cases averted with a low-energy diet intervention (1,642,209 people with BMI > 30) – long-term Weibull weight regain, probabilistic (5,000 simulations)

Disease	Men	Women	Total
IHD	-2,352 (-3,643 to -1,435)	-502 (-890 to -203)	-2,854
Stroke	-547 (-919 to -280)	-641 (-1,118 to – 290)	-1,188
Diabetes	-15,507 (-22,862 to -10,011)	-19,088 (-27,982 to -12,363)	-34,595
Colorectal cancer*	75 (20 to 142)	172 (103 to 260)	247
Liver cancer*	-13 (-47 to 14)	3 (-21 to 24)	-10
Kidney cancer	-8 (-34 to 16)	-23 (-48 to -4)	-31
Cirrhosis	-166 (-261 to -95)	-160 (-250 to -92)	-326

* *Cases of cancers were found to be higher due to the improved life expectancy caused by the intervention*

Base-case cost–utility results

Table 17 shows the probabilistic results for each population in the base case scenario over a lifetime period (Weibull weight regain and 3.5% discounting rate on both outcomes and costs). In general, the intervention proved to be cost-effective, with a cost per QALY below the NICE threshold of £20,000. Notably, the intervention is highly likely to be cost-effective (with a 100% probability) in the population affected by diabetes, as the advantages of remission are combined with the benefits of weight reduction. The only population where the cost-effectiveness is less certain (24%) is the mixed population living with overweight or obesity (people with BMI above 25). This is because the benefits of weight reduction are relatively lower in people with a lower BMI.

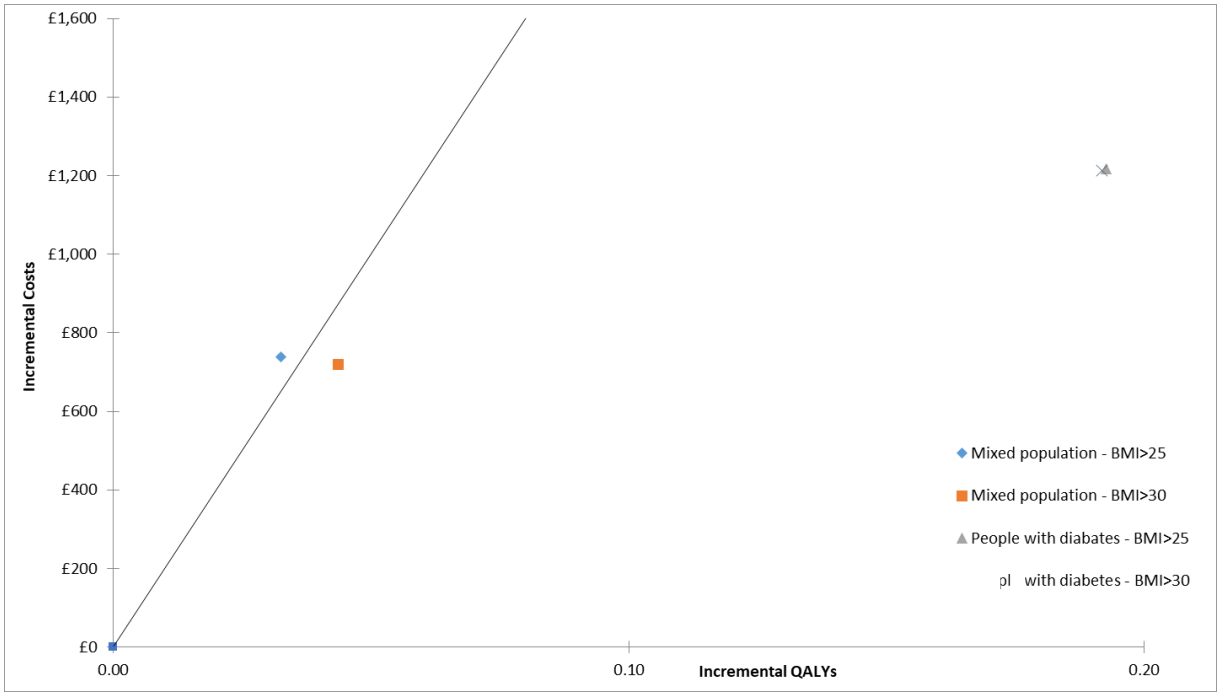
Table 17: Base case results TDR vs usual care – probabilistic (5,000 simulations), mean values with confidence intervals in brackets

Population	Incremental cost per person	Incremental QALYs per person	Cost per QALY	Probability of being cost-effective (20k)
Mixed population, overweight and obesity (BMI>25)	£739 (697 to 768)	0.032 (0.22 to 0.046)	**£22,742**	24%
Mixed population, obesity (BMI>30)	£718 (661 to 757)	0.044 (0.029 to 0.062)	**£16,456**	79%
People with diabetes, overweight and obesity (BMI > 25)	£1,217 (1,085 to 1,317)	0.193 (0.161 to 0.230)	**£6,317**	100%

Population	Incremental cost per person	Incremental QALYs per person	Cost per QALY	Probability of being cost-effective (20k)
People with diabetes and obesity (BMI > 30)	£1,212 (1,082 to 1,307)	0.192 (0.169 to 0.219)	**£6,318**	100%

Figure 20 illustrates the cost-effectiveness plane including all the four base-case scenario results. As mentioned above, only the scenario where the intervention is given to a mixed population who are living with overweight or obesity (blue triangle) lies above the £20,000 threshold line (the diagonal line).

Figure 20: Cost-effectiveness plane – base case scenario*, probabilistic



** Weibull weight regain and 3.5% discounting rate on both outcomes and costs*

HE3.2 Scenario analyses

Table 18 and **Error! Reference source not found.** illustrate the scenario analysis results in, respectively, a mixed population who are living with obesity and people with diabetes who are living with obesity. In the first population, when applying a linear weight regain instead than a Weibull regain, the intervention was found to be not cost-effective at a threshold of £20,000. However, it once again became cost-effective when the discounting rate was lowered to 1.5% to align with the rate used in the Kent study[18].

Table 18: Scenario analysis results - mixed population (BMI>30), probabilistic (5,000 simulations), mean values with confidence intervals in brackets

Population	Incremental cost per person	Incremental QALYs per person	Cost per QALY	Probability of being cost-effective
Base case*	£718 (661 to 757)	0.044 (0.029 to 0.062)	**£16,456**	79%
Linear weight regain	£752 (712 to 778)	0.029 (0.18 to 0.043)	**£26,327**	10%
Linear weight regain, Discount rates = 1.5%	£732 (681 to 767)	0.044 (0.027 to 0.066)	**£16,794**	72%

** Weibull weight regain and 3.5% discounting rate on both outcomes and costs*

In people with diabetes, the intervention remained cost-effective even when the more conservative assumption of linear weight regain was tested. This is because the greatest benefits in this population are driven by diabetes remission achieved in the first two years, which is not affected by the trajectory of weight regain.

Table 19: Scenario analysis results – people with diabetes (BMI>30), probabilistic (5,000 simulations), mean values with confidence intervals in brackets

Population	Incremental cost per person	Incremental QALYs per person	Cost per QALY	Probability of being cost-effective
Base case*	£1,212 (1,082 to 1,307)	0.192 (0.169 to 0.219)	**£6,855**	100%
Linear weight regain	£1,227 (1,107 to 1,318)	0.187 (0.164 to 0.214)	**£6,553**	100%
Linear weight regain, Discount rates = 1.5%	£1,216 (1,075 to 1,322)	0.237 (0.206 to 0.276)	**£5,123**	100%

** Weibull weight regain and 3.5% discounting rate on both outcomes and costs*

HE3.3 Discussion

HE3.3.1 Principal findings

This cost-utility analysis assessed the cost-effectiveness of a low-energy diet intervention and found that:

1. In a mixed population, a low-energy diet intervention is cost-effective in people living with obesity (BMI > 30 kg/m^2) but not in people living with overweight (BMI > 25 kg/m2). The results were found to be sensitive to the assumption on weight regain: when the more conservative scenario of linear regain was tested, the intervention was found to be not cost-effective in either group.

2. In people with diabetes, a low-energy diet intervention is cost-effective in people living with obesity (BMI > 30 kg/m^2) and people living with overweight (BMI > 25 kg/m^2). The results were found to be robust as the intervention remained cost-effective even when a linear weight regain was assumed.

The findings of this analysis are limited to the adult population and cannot be generalised to a paediatric population.

The analysis was specifically conducted on an English population using baseline characteristics derived from the Health Survey of England. As BMI distribution is country-specific, the findings might not be generalisable to other jurisdictions or countries.

In addition, these findings may not be generalisable to other diet interventions, particularly those that do not include a weight maintenance component. The trials informing this analysis, DIRECT, DROPLET, and DIADEM-I, incorporated a strong weight maintenance programme involving specialist follow-up and, in some cases, "rescue plans" for individuals experiencing a steep weight regain. As weight regain was identified as a crucial aspect of the analysis, it is likely that any diet intervention lacking similar efforts in preventing regain would not be cost-effective.

There is a real need of research focusing on long-term weight reduction and prevention of weight regain. While the 5-year data from DIRECT has offered valuable insights and enabled an approximation of the weight regain trajectory using a mathematical distribution, it is evident that more extensive and extended data is required to refine our estimates. Patient registries that follow individuals over an extended period present a promising opportunity for conducting longitudinal analyses to explore the trajectory of weight changes. Further efforts utilising real-world data are crucial in enhancing our understanding of this phenomenon and facilitating the effective implementation of weight management interventions.

HE3.3.2 Strengths of the analysis

The main strength of this analysis is the utilisation of the PRIMEtime model, which is a peer-reviewed model developed by Oxford university that has been used for multiple publications over the years. Therefore, the methodology, structure and main data inputs used in the model have already been validated elsewhere[6].

As the model was originally designed for population-level interventions, certain adaptations were necessary to facilitate its use in the current NICE economic evaluation. Baseline risks and characteristics were adjusted to reflect the population of interest using real-world data from the Health Survey for England (2017-2019). The HSE is an annual survey of a randomly selected sample of English residents comprising a wide range of socio-economic, demographic and health-related characteristics. A key advantage of using the survey for this analysis is the assurance of data reliability, as BMI measurements are not self-reported but rather obtained through follow-up visits conducted by trained nurses. Therefore, the population modelled in this analysis should closely reflect people accessing weight management services in England, which enhances the external validity of the results.

Although long-term data on weight regain is generally lacking, this analysis used academic-in-confidence 5-year data obtained by the principal investigators of DIRECT trial. Consequently, it was possible to estimate a weight regain trajectory using a mathematical model informed using that data. To our knowledge, this is the first analysis attempting to estimate weight regain using a "curve fitting" approach as previously published analyses have often relied on weight regain assumptions[5].

Lastly, similar to other non-communicable disease (NCD) models, PRIMEtime is a predictive risk model developed to translate risk factors, such as BMI, into tangible health outcomes. This allowed us to convert the weight reduction observed in the clinical review into estimates of disease prevention. BMI is a risk factor for several diseases in the long-term, yet the long-term health impact of weight reduction interventions is not easily observed within the limited time frame of a clinical trial. Therefore, using a predicted risk model appears to be justified when conducting analysis with a life time horizon.

HE3.3.13 Weaknesses of the analysis

Like other BMI-mediated NCD models, PRIMEtime focuses solely on consequences of obesity related to the diseases included in the analysis. It does not account for the direct effect of BMI on health and mortality, such as frailty, falls or limited mobility. Additionally, the model is constrained by the availability of data linking BMI and health conditions, so it may not encompass all potential BMI-related diseases. Consequently, the model might underestimate the overall impact of obesity on an individual's well-being. This is especially notable in terms of mortality, as the model's estimated hazard ratio of 1.2 falls towards the lower end of similar estimates reported in the literature[12, 32].

Another important limitation of PRIMEtime and other NCD models is the inability of incorporating the effect of time lag between exposure and disease outcome[24]. This generates two limitations. Firstly, as change in BMI are instantly translated into a change in risk, the model might overestimate short-term benefits of a weight reduction intervention as, in reality, health benefits of weight reduction would occur gradually over time. Secondly, the model does not consider lifetime exposure to the risk factor when calculating the risks. This might produce some distorting effects. For example, the well-established association between obesity and diabetes is often attributed to insulin resistance caused by high BMI levels[2], that forces the pancreas to produce more insulin. Over time, the pancreas will struggle to keep up with the increased demand, leading to high blood sugar levels and the eventual development of type 2 diabetes. This is a gradual process that requires time to develop into diabetes, and it can be reversed if an individual loses weight. However, since the model does not account for the duration of time spent in a particular weight category, this phenomenon is not adequately captured.

While predicting weight regain after an intervention has traditionally been addressed by imposing assumptions on its trajectory, this analysis took a different approach by adopting a "distribution fitting" method based on academic-in-confidence data from DIRECT. This is a more evidence-based approach to predict weight regain but it is subject to some limitations:

1. An assumption was made that weight regain follows a two-parameters Weibull distribution. This was based on the data from DIRECT that showed a decreasing trend over time in weight regain. However, other distributions are available in the literature and it is challenging to determine the true distribution describing a phenomenon. If a Weibull is inappropriate to describe weight regain, this might lead to inaccurate parameters estimation and flawed results.
2. The accuracy of a distribution heavily relies on the amount of data available. In general, having a large dataset improve the reliability of the estimated parameters and increased the changes of capturing the true distribution. For this analysis, only 5-year data from DIRECT were observed, which could be too few to estimate the true distribution.
3. The distribution parameters were estimated using data from a single trial, DIRECT, as it was the only available long-term dataset on people who underwent a low-energy diet intervention. It is important to acknowledge that DIRECT had strict inclusion criteria and enrolled only individuals with diabetes, which raises the possibility that the trial may not be entirely representative of the broader population. This could distort the estimated parameters leading to inaccurate results.

Due to limitations mentioned above, a scenario analysis using a linear regain commonly assumed in the literature was included.

Low-energy total diet replacements can be challenging for some individuals as these typically involve replacing most or all regular meals with specially formulated low-energy shakes, soups, bars or other products. In some cases, people might experience feeling of hunger and reduced satisfaction after eating which might affect compliance with the diet plan. Moreover, people could also experience low energy level and fatigue which could impact daily activities and quality of life. Furthermore, it was mentioned by the committee that a strict total diet

replacement might have a social and psychological impact as they may limit participations in social activities that revolve around food. Increased loneliness and psychological distress due to the strict nature of the diet could also affect quality of life. Due to the lack of data available, the model could not incorporate the direct impact of diets on quality of life. Consequently, it is possible that the analysis is overestimating total benefits by disregarding short-term reductions in quality of life caused by the intervention itself. These reductions are expected to be temporary, lasting only for the duration of the diet, so it is unlikely that they would significantly affect the conclusion of the analysis.

The model does not include states for composite CVD events or combinations of two or more events. This is primarily due to a lack of available data to accurately estimate risks, healthcare costs and quality of life for people who have experienced multiple events. However, this is not expected to represent a significant limitation as the model accurately estimates the incidence of diseases and deaths that occur in the cohort and does not need to predict the pathway for individual patients.

Finally, the original PRIMEtime model did not incorporate the phenomenon of remission from any disease, as there was insufficient evidence linking weight reduction to remission from NCDs. However, remission in this analysis was allowed for people with diabetes, based on the findings from the DIRECT trial that demonstrated an association between weight loss and diabetes remission. Remission could be achieved from the other diseases too, suggesting that the model could be underestimating the benefits of intervening. Furthermore, the model does not capture the severity of the diseases. Even in cases where remission is not achieved, weight reduction might improve the symptoms of a person with a particular disease, which is a factor not accounted for.

HE3.3.4 Comparison with other CUAs

Two economic evaluations were conducted on DROPLET and DIRECT trials.

Kent and colleagues conducted a study on DROPLET[18] using a similar version of the PRIMEtime model and found that the intervention was cost-effective with a cost per QALY of £12,955. The analysis assumed that weight is fully regained over five years and that the discounting rate for future benefits and costs of 1.5%. Using the same assumptions, the present analysis found the intervention cost-effective as well with a cost per QALY of £16,794 . However, the NICE reference case requires a discount rate of 3.5% for both costs and health outcomes. Using these rates and the linear regain scenario, the model found the intervention not cost-effective in those with a BMI > 25 kg/m^2 (cost per QALY = £26,327).

Xin and colleagues conducted a cost-utility study on DIRECT[30] and found that the intervention dominated standard care (i.e. cost less and was more effective than standard care). These results align with the present analysis that found the intervention very cost-effective in people with diabetes, with a cost per QALY of £6,855. However, this study found that the intervention is still more expensive than standard care.

HE3.4 Conclusions

This cost-utility analysis found that a low-energy diet intervention is highly likely to be cost-effective in people with diabetes. These findings remain robust to all scenario analyses and primarily driven by the benefits of weight reduction on diabetes remission observed in DIRECT trial.

Moreover, this analysis suggested that a low-energy diet intervention is likely to be cost-effective in people with or without diabetes and a BMI above 30 kg/m^2. However, these findings were highly sensitive to the assumptions on weight regain: when a more conservative scenario was tested, the intervention ceased being cost-effective.

Finally, this analysis found that a low-energy diet intervention is unlikely to be cost-effective in people with or without diabetes and a BMI above 25 kg/m^2. These findings remain robust in the scenario analysis and indicates that the intervention should be targets toward those who can derive the greatest benefit from it, such as people with diabetes or living with obesity.

HE4 References

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