NICE National Institute for Health and Care Excellence

# Disease-specific reference case extension: Management of overweight and obesity in adults

## Appendix B: Literature review of economic evaluations of interventions for obesity

# Contents

# The rationale for the review

The aim of this pragmatic review was to gain an understanding of how obesity has been modelled in the literature and summarise existing economic modelling approaches used in cost-effectiveness analysis for obesity.

# Methods

Initially, the published NICE guidance and technology appraisals (TAs) that had a primary indication of obesity were identified and reviewed, specifically: TA664 (liraglutide), TA875 (semaglutide), TA1026 (tirzepatide) and NG246 'Overweight and obesity management'. Each of these included a systematic review of health economic evaluations of interventions for obesity as well as de novo health economic models.

The most recent review of health economic evaluations of treatment for obesity in the TAs was conducted as part of the tirzepatide TA. This was a systematic literature review of databases (Embase, MEDLINE, INAHTA, NHSEED) and HTA agencies of cost effectiveness analyses for obesity medicines up to October and December 2022 respectively. 16 economic evaluations were included in this review, of these, 6 orlistat, while 5 evaluated liraglutide and 5 semaglutide. Models in this review were primarily Markov models (thirteen studies), while the remaining utilised individual patient simulation (IPS) models (three studies). In the TA, detailed reporting was only provided for the liraglutide and semaglutide TA models as these were the only two published in the last decade with an NHS focus.

In the guideline NG246, all systematic literature reviews were done by review question and therefore limited to interventions listed in the review question protocol. The only studies of relevance were:

- Evidence review F on diet, which searched databases (Embase, MEDLINE, EconLit, INAHTA, HTA, NHSEED) up to April 2023. Three economic evaluations were included: one was a within trial analysis and two were

models using the PRIMEtime model (including the NICE de novo model for that guideline).

- Referral to bariatric surgery which searched databases (Embase, MEDLINE, INAHTA, EconLit, NHSEED) up to February 2022. Four economic evaluations were included comparing bariatric surgery to no intervention or conventional treatment. Three were Markov models, all were UK based and published in the last decade (2016-2021).

A top-up search was undertaken to identify any further publications of studies assessing the cost-effectiveness of interventions for obesity that utilised economic modelling approaches, the following databases were searched Embase (Ovid), MEDLINE (Ovid), and INAHTA.

The database search was limited to English language studies published from February 2022 to February 2025. This start date was selected to ensure any publications since the 'referral to bariatric surgery' review cut-off date are captured. This would also ensure any publications after the tirzepatide TA and NG246 diet search cut offs were also identified.

Key search terms combined terms for the target condition (obesity) and economic evaluations. Citation lists of systematic literature reviews were reviewed to identify additional relevant publications. In addition to this top-up search, HTA websites have been checked for obesity-related economic models, the following HTA organisations were included:

- Canada's Drug Agency (CDA-AMC) in Canada
- Institute for Quality and Efficiency in Health Care (IQWiG) in Germany
- Institute of Clinical and Economic Review (ICER) in the US
- NICE in England
- Zorginstituut Nederland (ZIN) in the Netherlands.

The inclusion and exclusion criteria are presented in **Table 1** and the full search strategy is provided in the **Appendix A1. Search strategies**.

**Table 1. Inclusion and exclusion criteria for studies**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | Persons with a diagnosis of obesity. | Studies of persons where neither the full population nor a defined subpopulation have a diagnosis of obesity. |
| Interventions | Interventions for treatment of obesity. | Studies assessing diagnosis or screening of obesity, but not treatment. |
| Comparators | Any intervention or no intervention. | None. |
| Outcomes | Total costs and health outcomes, incremental cost-effectiveness ratios (ICERs). | Studies that do not report any of the outcomes of interest. |
| Study type | Full or partial economic evaluations that include an economic modelling component. | Epidemiological studies, burden of illness studies and other non-comparative cost studies, poster abstracts that did not provide sufficient methodological detail, letters to the editor, commentaries. |

**Abbreviations**: ICER, incremental cost-effectiveness ratio

EPPI Reviewer 5 was used to export and store records from each database. Results were screened against the selection criteria based on their titles and abstracts. Records that potentially met the inclusion criteria were ordered and the full paper reassessed against the selection criteria. All includable studies were extracted. Data were extracted into prespecified tables developed in Microsoft Excel. The data captured was around the study characteristics (country, setting, interventions and comparator), methods (type of economic evaluation, analysis approach and perspective, time horizon, cycle length, discount rate, cost items included, health

outcome measures, data sources for effectiveness and utility values) and authors' self-reported limitations. The review aimed to summarise modelling approaches and challenges, and not to identify the most cost-effective treatments for obesity; therefore, cost-effectiveness outcomes were not reported, but where available, key model drivers were extracted.

A narrative synthesis was established around the methodological approaches and assumptions of the included studies and any limitations highlighted by the authors.

# Results

## 1.1 Overview of Included Studies

The database search yielded a total of 3,185 hits after deduplication. Of those, 3,149 were excluded based on their title and abstracts. The targeted search of HTA organisations' websites identified 5 additional HTA reports. Also included in the extraction table were the 4 models identified in the bariatric surgery evidence review for NG246. Therefore, a total of 45 publications across the database search and targeted search were reviewed in full.

After reviewing the full publications, 26 studies that reported economic models for the treatment of obesity were finally included. Of these, five were HTA reports: three NICE TAs, one NICE guideline and one ICER model (US HTA). Most of the studies were carried out in the UK setting (n=11), followed by the US (n=7), and Canada (n=2).

A PRISMA flowchart outlining the different stages of identification and selection of studies is presented in
**Figure 1**.

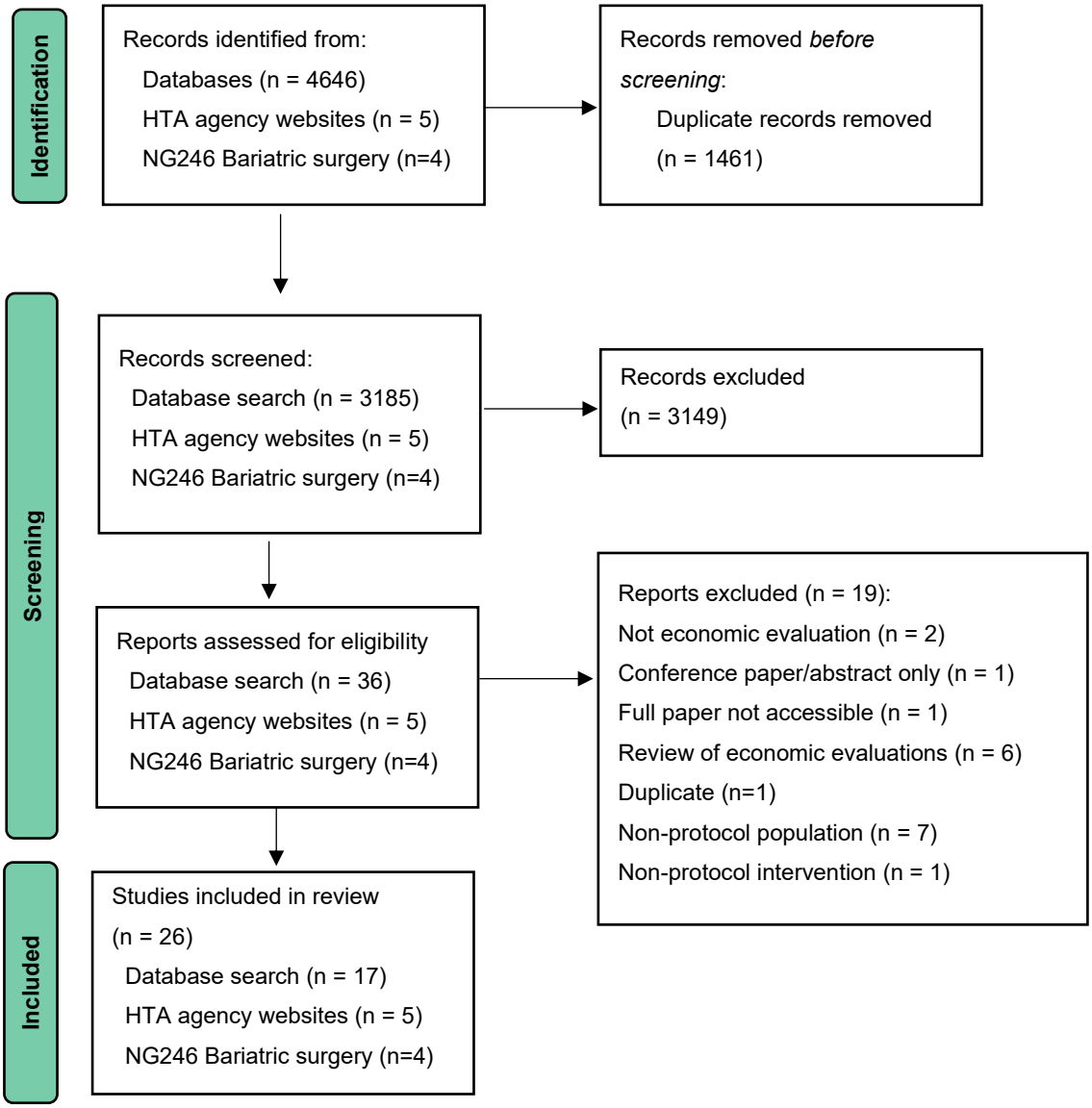


**Figure 1. PRISMA flowchart for identification and selection of studies**

Of these 26 papers, 15 studies evaluated anti-obesity pharmacotherapy, and four studies assessed bariatric surgery as a treatment for obesity. Three studies examined a combination of interventions, including pharmacotherapy, lifestyle modification, and dietary intervention. Additionally, two studies focused solely on lifestyle changes (such as self-managed dietary plans and exercise), and two studies evaluated dietary interventions alone (such as calorie reduction and structured nutrition plans). The characteristic is included studies is provided in the **Appendix A2. Characteristics of included studies.**

**Targeted Populations**

The populations modelled in the included studies varied by BMI thresholds, presence of comorbidities, and diabetes status. For pharmacotherapy studies, the most commonly assessed populations included adults with a BMI ≥30 kg/m² with at least one weight-related comorbidity as the base case. Other populations modelled included adults with a BMI ≥35 kg/m² with non-diabetic hyperglycaemia and high cardiovascular disease (CVD) risk, adults with a BMI ≥40 kg/m² (assessed in a scenario analysis), adults with a BMI ≥27 kg/m² with at least one comorbidity, and adults with a BMI ≥25 kg/m² in subgroup analyses.

For dietary intervention studies, populations included individuals classified as overweight (BMI >25 kg/m²) and those with obesity (BMI >30 kg/m²). Studies focusing on lifestyle modifications targeted individuals with a BMI ≥28 kg/m². Studies evaluating bariatric surgery, or a combination of surgery and pharmacotherapy, primarily included individuals with a BMI >35 kg/m² or BMI >40 kg/m².

Some studies included both people with and without diabetes: four studies only included people with both obesity and diabetes, and two studies evaluated both individuals with diabetes and those without. In contrast, thirteen studies excluded populations with diabetes, and eight studies did not report participants' diabetes status.

**Interventions and comparators**

Among the 15 studies that evaluated anti-obesity pharmacotherapy, some assessed a single agent, such as an incretion agonist, while others evaluated multiple available anti-obesity drugs, depending on the study context. Pharmacotherapy interventions were most commonly compared to standard lifestyle modification (diet and exercise) or against other pharmacological agents.

For studies assessing bariatric surgery, the comparator was typically standard lifestyle modification. In studies evaluating dietary interventions for obesity

management, the comparator was a conventional diet plan. Studies investigating self-management interventions compared these strategies with no intervention.

### 1.2 Types of economic models and analysis approaches

Most of the included studies conducted cost-utility analysis (n=23) using costs and quality-adjusted life years (QALYs) as outcomes to compare the costs and health benefits of different interventions. Three studies conducted cost-effectiveness analyses, measured by a wide range of health outcomes or using life-year gained.

All included studies were model-based economic evaluations. Almost half of the studies (n=14) employed a Markov state-transition cohort approach. Four studies used a microsimulation modelling framework and one study was a Markov model which used an individual patient simulation rather than a cohort. Three studies applied a decision analytic model. One study utilised a discrete event simulation model, and one study incorporated a Mendelian randomisation approach to tackle the causal effects of potential risk factors.

Time horizon was reported in almost all studies. Among those studies, long-term horizons (such as 20 years, 30 years, 40 years) and lifetime horizon were frequently used. Other relatively short horizons (such as 1 year, 17 months, 5 years and 10 years) were used in some studies. In studies where the time horizon exceeded one year, costs and benefits were discounted, most commonly at 3.5% per annum, depending on the study's settings.

For the cycle length, half of the studies (n=13) adopted a 1-year cycle, while some studies had an alternative approach to incorporate pharmacotherapy treatment durations, discontinuations, and stopping rules. For example, 4-week cycle for the first 2 years, followed by an annual cycle length for the rest of the lifetime time horizon. However, the cycle settings have heterogeneity across these studies, where different early cycle breakdowns were used.

Half of the studies conducted their evaluations from a healthcare system perspective (N=13), considering only direct healthcare costs, including medications, surgery, treatments for complications and adverse events, and outpatient hospital visits. The rest were conducted from a societal perspective (n=2) or from both healthcare and societal perspectives (n=11), and included non-medical costs (such as social care costs) and productivity loss.

### 1.3 Model structures and health states used

The included model-based economic evaluations commonly relied on surrogate outcomes to inform effectiveness within the models. Of the 15 studies using a Markov state-transition method, eight studies used risk equations to estimate transition probabilities for health states (such as type 2 diabetes mellitus (T2DM) status and cardiovascular disease (CVD) events). Four studies, based health state transitions solely on BMI, establishing health states defined by different obesity levels. Additionally, five studies incorporated hard clinical outcomes, directly tracking clinical events observed in the trials to inform health state transitions or decision analytical models.

A few different model structures were identified in terms of health states used. One is the Core Obesity Model (Lopes et al. 2020 and Lopes et al. 2021) which is used in 6 studies for pharmacotherapy, including TA guidelines. In this specific model, 11 health states have been developed based on T2DM status and CVD events. Patients were assumed to enter the models at the stages of normal glucose tolerance or prediabetes (non-diabetic hyperglycaemia or non-diabetic hyperglycaemia reversal) and T2DM. Then, they would enter the stages of first complication, which includes 4 states: Post acute coronary syndrome (ACS), or Post stroke, or T2DM + Post ACS, or T2DM + post stroke. After the first complications, they could transition to further complication states, including Post ACS + post stroke or T2DM + post ACS + post stroke. Among these studies with the Core Obesity Model, one study conducted an additional first complication state: cancer and T2DM + Cancer, considering the cancer development in a scenario analysis. In any health state, the following could

occur: sleep apnoea or knee replacement or bariatric surgery. The last health state is death. Of note, no liver disease health states were included.

There are a few other studies that also constructed their health states in a way that captured the complex nature of obesity and its associated comorbidities over time. Among these models, one study (Atlas et al. 2022) had a Markov structure beginning with patients in a 'No DM' health state. From the first cycle onward, patients could transition to several cardiovascular-related health states, including myocardial infarction (MI), stroke, combined MI and stroke, or other cardiovascular diseases (e.g., peripheral artery disease, angina, and transient ischemic attack), with or without developing diabetes. Heart failure was modelled as a consequence of prior MI due to its strong causal relationship with obesity. The model assumed optimal blood pressure control in all patients and did not include non-ischemic pathways to heart failure. Patients could transition to a death state from any health state. One model for a surgical intervention (Galvain et al. 2021) was distinct from the above structures, with patients able to transition between diabetes-related health states (with T2DM, without T2DM, or in T2DM remission), with ongoing transitions possible between T2DM and remission. Additionally, patients could simultaneously transition through mutually exclusive health states for major comorbid conditions, including stroke, MI, and cancer. For patients undergoing bariatric surgery, the model incorporated pre-Markov allocations for surgical complications, reoperations, and 30-day mortality.

Another identified model (NICE TA1026), which conducted an individual patient simulation for Markov state-transition, also used T2DM status and other related events for health states. Patients were assumed to start at the stages of no CVD events (Normal glucose tolerance or Pre-DM). Then, they would have the following clinical events, including temporary reversal of prediabetes, stroke, MI, angina, sleep apnoea, non-alcoholic fatty liver disease (NAFLD), and T2DM. Of note, liver disease and sleep apnoea health states were included as ongoing status. Other clinical events modelled as one-off effects include knee replacement, bariatric surgery and treatment-related adverse events (AEs). These can occur to patients in any state at any time with a specified probability, which may depend on existing comorbidities or

surrounding conditions. Finally, a death state is included, which includes CVD-related or non-CVD death.

One identified model from NG246, the PRIMEtime (Preventable Risk Integrated ModEl) model. It is a computer simulation used to assess the impact of dietary factors on the risk of chronic diseases, including cancer and T2DM. It is a multi-cohort Markov life table model that simulates the natural history of disease over time within a population, incorporating states such as healthy (alive without disease), disease onset, and death (from all causes or specific diseases). The model captures the progression of obesity-related comorbidities, including ischaemic heart disease (IHD), stroke, T2DM, cirrhosis, and several cancer types (breast, colorectal, kidney, and liver cancer). Cancer incidence is derived from national registry data and modelled explicitly, with transitions accounting for age- and sex-specific risks, case fatality, and mortality rates to estimate population-level health and economic outcomes.

Besides health states based on weight-related comorbidities, some studies based on the degree of weight loss or obesity status (i.e. based on BMI) for their health states in the models (Papantoniou and Maniadakis 2025, Haseed et al. 2024, Mital and Nguyen 2023).

As outlined, current models are generally designed to account for weight-related comorbidities, aiming to capture the complex nature of obesity. These comorbidities, which are either caused or worsened by excess body weight, often include hypertension, type 2 diabetes mellitus, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD). Some studies considered these comorbidities when identifying and segmenting populations most likely to benefit from interventions. These conditions not only influence baseline risk but also affect transition probabilities in models of disease progression, ultimately shaping outcomes such as QALYs and healthcare costs.

## 1.4 Approaches to inform effectiveness in models

The treatment effect of the intervention can be incorporated through a reduction in either the intermediate clinical outcomes or the final clinical outcomes. Most included studies (n = 18) used surrogate outcomes, such as weight loss or weight change converted to body mass index (BMI) change, to measure treatment effects in their models. These surrogate outcomes are widely used in the evaluation of overweight and obesity interventions due to their association with the risk of developing chronic conditions. Weight loss is particularly linked to a lower incidence of T2DM, cardiovascular disease, and other long-term health issues. Other surrogate outcomes are also used, including systolic blood pressure, total cholesterol and high-density lipoprotein. These surrogate measures are particularly helpful when direct clinical endpoints (like heart attacks or mortality) are not observed during the trial period. Of the studies that used surrogate outcomes to inform effectiveness in models, 18 studies derived their effectiveness data from clinical trials or meta-analyses. Five studies measured the treatment effect by BMI changes and derived their effectiveness data from a mixture of national dataset and meta-analyses. The clinical trials assessing the effects of drugs on surrogate markers such as blood pressure and BMI were not specifically powered to detect adverse cardiovascular events in people with obesity, such as mortality.

In contrast, three studies used direct clinical outcomes to inform their models. Health outcomes and state transitions were based on actual clinical events observed during the trials, using survival equations derived from clinical trial data, such as that from the SELECT trial (Lincoff et al. 2023). For instance, one study (McEwan et al. 2025) modelled risks of cardiovascular events (such as MI), progression to T2DM, chronic kidney disease (CKD), and mortality. Another study (Zomer et al. 2024) defined health states as alive with CVD, alive with recurrent CVD, and dead, while a third study (Rennert-May et al. 2025) included states such as alive without complications, experiencing a cardiovascular event (such as ischaemic stroke, heart failure hospitalisation, myocardial infarction), and dead. Statistical approaches, including joint and independent survival models, were selected based on model fit.

In some of the non-pharmacotherapy studies, trajectories of BMI and other risk factors were used to estimate the impact of weight loss and weight loss maintenance

on a range of health conditions including CVD, T2DM, osteoarthritis and depression in their simulation models (Bates et al. 2022, NG246, Arrospide et al. 2022).

### 1.5 Risk factors

In many cases, it is not feasible to directly measure final outcomes. Even when such measurements are available, they are often limited to short-term observations. Consequently, extrapolation is necessary to estimate long-term risks, particularly in models with a lifetime horizon. Some studies used existing risk equations to estimate the probability of clinical events such as MI, angina or stroke and the risk of developing T2DM in their models, as well as mortality.

Risk equations incorporate various factors, such as characteristics, behaviours, and exposures that influence the likelihood of developing specific health conditions. Several established tools are commonly used in the UK context, as well as current TAs:

- QDiabetes is a UK-developed clinical risk prediction model estimating an individual's 10-year risk of developing type 2 diabetes. It incorporates variables such as age, BMI, ethnicity, smoking status, family history, and comorbidities like hypertension and cardiovascular disease.

- The Framingham Risk Equation, developed from the US-based Framingham Heart Study, predicts 10-year cardiovascular risk using factors such as age, sex, cholesterol levels, blood pressure, smoking status, and diabetes. However, it may underestimate risk in more deprived populations, as it does not account for socioeconomic factors.

- QRisk3, another UK-based tool, predicts 10-year cardiovascular disease risk and includes a broader range of variables. In addition to traditional clinical factors, it accounts for ethnicity, socioeconomic deprivation, and conditions such as severe mental illness and chronic kidney disease, enhancing its relevance across diverse populations.

The detailed information regarding the use of risk equations in the TAs is provided in the **Appendix A3: Risk equations used in TAs.**

Despite the use of risk equations to estimate long-term outcomes, concerns have been raised in TAs regarding their appropriateness and limitations. Risk equations typically rely on relative treatment effects applied to surrogate endpoints to project long-term cardiovascular outcomes. This approach introduces uncertainty, particularly when extrapolating beyond the duration of clinical trials. Furthermore, these models were not originally developed to estimate long-term risk in the context of interventions with time-limited benefits, which may compromise their validity in such scenarios. In the case of incretin agonists, the full cardiovascular benefit may be underestimated when using risk equations rather than direct clinical outcomes. This is especially relevant if the intervention exerts effects through an unknown or complex mode of action not captured by the model inputs. Despite these methodological uncertainties, the Evidence Assessment Groups (EAG) for the incretin agonist TAs concluded that risk equations remain the only feasible approach currently available for estimating long-term cardiovascular outcomes in the absence of direct evidence.

## 1.6 Costs and Quality of Life

Costs incorporated in the models varied based on the interventions and perspectives defined. Direct medical costs included expenses related to disease conditions, such as treatments, diagnostic procedures, and healthcare resources used. Indirect costs were associated with productivity losses due to illness. Most of the studies that evaluated pharmaceutical treatments included treatment costs (acquisition cost of pharmacological treatment and the cost of diet and exercise), obesity monitoring cost, cost of obesity-related complications, costs of treatment-related adverse events, bariatric surgery costs, etc.

Only five studies that evaluated incretin agonist drugs considered severe gastrointestinal (GI) AEs in the economic evaluation model. One study considered AE discontinuation mainly in year 1 and 1% annually thereafter (NICE TA1026). The

other study applied a percent severity multiplier to capture the proportion of patients with severe adverse events (Kim et al. 2022).

For the studies that evaluated surgery, they considered the intervention costs, including costs of surgery, repeat surgery and associated AEs from surgery.

The cost elements included in the model depended on the model structure and health states, for example where the model structure included health states for individual obesity-related comorbidities, the cost of managing the comorbidity was attributed to this health state. In contrast, where the structure included health states by BMI category, an average cost associated with healthcare usage for people in that BMI category was applied. In both examples, the costs are based on published sources, such as literature, NHS reference costs or UKPDS costs. No evidence of the use of regression analyses on patient level data were seen.

With respect to outcome measures, most studies reported generic health outcomes, most commonly QALYs. Fifteen studies derived utility values based on BMI and other risk factors such as age and sex. The most frequently used approach involved assigning baseline utility values that varied according to BMI, while incorporating health-related quality of life (HRQoL) decrements (disutilities) associated with comorbidities and acute events. In seven studies, utility estimates were generated by assigning utility weights to defined health states. Two studies obtained utility values directly from clinical trial data. However, the methodologies used to derive these utility values were often inadequately described. Additionally, two studies did not report their approach to utility estimation.

In the PRIMEtime model in the UK (Briggs et al. 2019), disease-specific treatment costs are sourced from NHS England Programme Budgeting Data, while unrelated future healthcare costs are estimated using NHS cost curves. Utility values (baseline EQ-5D and disease-specific decrements) are taken from Sullivan et al. 2011 and adjusted for age and multimorbidity. These are used to estimate QALYs over time, accounting for disease onset, recovery, and mortality. PRIMEtime model also used a

collaborative analysis of 57 prospective studies to capture the impact of BMI on all cause and cause-specific mortality (Prospectives Studies Collaboration 2009).

### 1.7 Model uncertainty and sensitivity analysis

In the current obesity models, several assumptions introduce uncertainty that may impact the robustness of the economic evaluation.

- Weight rebound/regain assumptions

Assumptions regarding weight regain following treatment discontinuation represent a key source of uncertainty in obesity modelling. Ten studies considered treatment duration, with most assuming weight regain occurs over a 2-year period after stopping treatment. This was particularly relevant for liraglutide and semaglutide, which were only evaluated within specialist weight management service which allow a maximum duration of 2 years in the UK. However, the pattern and rate of weight regain varied across studies, reflecting the lack of long-term data to support these assumptions. Evidence from trials such as SURMOUNT-1 (Jastreboff et al. 2022) and SELECT (Lincoff et al. 2023) suggests that weight loss from pharmacological interventions slows over time and may stabilise, similar to patterns observed with lifestyle interventions. Despite this, assumptions about weight regain remained contentious and influential in recent TAs, including those for semaglutide and tirzepatide. The committee for tirzepatide preferred a 2-year regain period, informed by data from STEP-1 (Wilding et al. 2021), although this remains an area of considerable uncertainty requiring further exploration through scenario and sensitivity analyses.

- Impact on prediabetes

Some models included prediabetes as a baseline comorbidity in the analyses, with the potential for reversal following weight loss. Notably, the Core Obesity Model (Lopes et al. 2020 and Lopes et al. 2021) assumed no transition from prediabetes to T2D following a CVD event. Additionally, one study assumed individuals who revert to normal glucose tolerance would relapse into prediabetes after three years, despite

limited long-term evidence to support this rate of recurrence (NICE TA875). However, similar to assumptions around weight regain, there is a lack of long-term data to accurately predict the recurrence of prediabetes.

- Impact on diabetes

Diabetes remission and relapse is another source of uncertainty. Interventions that reduce weight have shown to increase diabetes remission (DIRECT trial, Lean et al. 2024). Some of these people will relapse but, with no long-term data, published HE analyses can only rely on uncertain predictions (Xin et al. 2019).

# Discussion

This pragmatic review was conducted to gain an understanding of how obesity has been modelled in the economic literature. This review summarises the modelling approaches used in cost-effectiveness analyses and provides background information that helped to inform the development of the NICE obesity reference case extension. The review identified substantial heterogeneity in model structures and health states, reflecting differences in research objectives, study perspectives and clinical settings. The choice of model structure and health states was often influenced by the intervention type (e.g. pharmacotherapy, surgery, or lifestyle), the population under consideration, and the specific policy or clinical questions being addressed. Many models used surrogate outcomes to estimate long term health outcomes, with a variety of different risk equations utilised. The models identified highlighted the limited evidence currently available to capture treatment effects over time, including weight regain following treatment discontinuation. Assumptions were often needed to inform these treatment effects over time. Discontinuation and weight regain appear to be key drivers in the model results. Finally, there were inconsistencies in how quality of life, healthcare resource use, and costs were captured across economic models.

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# Appendix

## A1. Search strategies

| Database: MEDLINE |
| --- |
| Strategy used:<br>Ovid MEDLINE(R) ALL <1946 to February 20, 2025><br><br>1 exp *obesity/ or Obesity Management/ or overweight/ or *adiposity/ 215779<br>2 (obes* or preobese* or overweight* or over-weight* or adiposity*).ti,ab. 449999<br>3 (weight* adj1 (loss* or management* or reduc* or status*)).ti,ab. 146668<br>4 (("body mass ind*" or "body fat ind*" or BMI or BFI) adj1 (loss* or management* or reduc* or status*)).ti,ab. 6458<br>5 or/1-4 569459<br>6 Economics/ 27545<br>7 Value of life/ 5834<br>8 exp "Costs and Cost Analysis"/ 276561<br>9 exp Economics, Hospital/ 26122<br>10 exp Economics, Medical/ 14458<br>11 Economics, Nursing/ 4013<br>12 Economics, Pharmaceutical/ 3156<br>13 exp "Fees and Charges"/ 31621<br>14 exp Budgets/ 14320<br>15 budget*.ti,ab. 39118<br>16 cost*.ti. 155686<br>17 (economic* or pharmaco?economic*).ti. 66785<br>18 (price* or pricing*).ti,ab. 59288<br>19 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. 238100<br>20 (financ* or fee or fees).ti,ab. 181168<br>21 (value adj2 (money or monetary)).ti,ab. 3359<br>22 or/6-21 803708 |

| | | |
|---|---|---|
| 23 | 5 and 22 | 11769 |
| 24 | letter/ | 1288009 |
| 25 | editorial/ | 720897 |
| 26 | news/ | 229814 |
| 27 | exp historical article/ | 415339 |
| 28 | Anecdotes as Topic/ | 4747 |
| 29 | comment/ | 1047940 |
| 30 | (letter or comment*).ti. | 209889 |
| 31 | or/24-30 | 2994472 |
| 32 | randomized controlled trial/ or random*.ti,ab. | 1731726 |
| 33 | 31 not 32 | 2967228 |
| 34 | animals/ | 7604929 |
| 35 | exp Animals, Laboratory/ | 988284 |
| 36 | exp Animal Experimentation/ | 10664 |
| 37 | exp Models, Animal/ | 674157 |
| 38 | exp Rodentia/ | 3686001 |
| 39 | (rat or rats or mouse or mice or rodent*).ti. | 1521410 |
| 40 | or/34-39 | 7736162 |
| 41 | 40 not humans/ | 5396425 |
| 42 | 33 or 41 | 8262949 |
| 43 | 23 not 42 | 11114 |
| 44 | limit 43 to english language/ | 10716 |
| 45 | limit 44 to ed=20220102-20250224 | 1713 |
| 46 | limit 45 to dt=20220102-20250224 | 1514 |
| 47 | 45 or 46 | 1713 |

| **Notes:** |
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| **Database: Embase** |
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| Strategy used:<br>Embase <1974 to 2025 February 20> |

1 exp *obesity/ or obesity management/ 317674
2 (obes* or preobese* or overweight* or over-weight* or adiposity*).ti,ab. 664203
3 (weight* adj1 (loss* or management* or reduc* or status*)).ti,ab. 233019
4 (("body mass ind*" or "body fat ind*" or BMI or BFI) adj1 (loss* or management* or reduc* or status*)).ti,ab. 11218
5 or/1-4 867130
6 Health economics/ 36963
7 exp health care cost/ 363687
8 exp Fee/ 45903
9 exp Budget/ 35813
10 Funding/ 82263
11 budget*.ti,ab. 51286
12 cost*.ti. 207362
13 (economic* or pharmaco?economic*).ti. 82545
14 (price* or pricing*).ti,ab. 80041
15 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. 321475
16 (financ* or fee or fees).ti,ab. 259403
17 (value adj2 (money or monetary)).ti,ab. 4452
18 or/6-17 1158073
19 5 and 18 23184
20 letter.pt. or letter/ 1364035
21 note.pt. 997145
22 editorial.pt. 825872
23 case report/ or case study/ 3144520
24 (letter or comment*).ti. 253567
25 or/20-24 6053005
26 randomized controlled trial/ or random*.ti,ab. 2290127
27 25 not 26 5989264
28 animal/ 1681525

| | | |
|---|---|---|
| 29 | nonhuman/ | 7984031 |
| 30 | exp Animal Experiment/ | 3291780 |
| 31 | exp Experimental Animal/ | 880084 |
| 32 | animal model/ | 1877447 |
| 33 | exp Rodent/ | 4238544 |
| 34 | (rat or rats or mouse or mice or rodent*).ti. | 1691317 |
| 35 | or/28-34 | 10540539 |
| 36 | 35 not human/ | 7473388 |
| 37 | 27 or 36 | 13295259 |
| 38 | 19 not 37 | 21048 |
| 39 | conference*.db,pt,su. | 6165894 |
| 40 | 38 not 39 | 12605 |
| 41 | limit 40 to english language/ | 11999 |
| 42 | limit 41 to dc=20220101-20250224 | 2789 |
| 43 | limit 41 to dd=20220101-20250224 | 2558 |
| 44 | 42 or 43 | 2795 |

**Notes:**

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**Database: INAHTA**

Strategy used:

English language and date limits applied results reduced to 138

| | | | |
|---|---|---|---|
| 8 | #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 | 1316 | February 24 2025 2:29 PM |
| 7 | (body mass index or body fat index or BMI or BFI)[Title] OR (body mass index or body fat index or BMI or BFI)[abs] | 973 | February 24 2025 2:29 PM |
| 6 | (weight)[Title] AND (loss* or management* or reduc* or status*)[Title] | 49 | February 24 2025 2:24 PM |

| | | | |
|---|---|---|---|
| 5 | (weight)[abs] AND (loss* or management* or reduc* or status*)[abs] | 311 | February 24 2025 2:23 PM |
| 4 | "Adiposity"[mh] | 2 | February 24 2025 2:20 PM |
| 3 | "Overweight"[mh] | 18 | February 24 2025 2:19 PM |
| 2 | "Obesity Management"[mh] | 23 | February 24 2025 2:19 PM |
| 1 | "Obesity"[mh] | 263 | February 24 2025 2:10 PM |

**Notes:**

## A2. Characteristics of included studies

**Tabe A2-1 Pharmacological treatments evaluated in HTAs**

| HTA agency, Report number, year, country | Population | Intervention | Comparator | Model type, cycle length, time horizon, Perspective | Health states | Model drivers/ key assumption or limitation |
|---|---|---|---|---|---|---|
| TA664 (NICE 2020), UK | BMI ≥35 kg/m2, non-diabetic hyperglycaemia, high risk for CVD | Liraglutide | Diet and exercise alone | Markov cohort model, 1-year, 40 years, healthcare perspective and social services perspective | 10 health states<br>1. Normal glucose tolerance,<br>2. Pre-DM<br>3. Type 2 DM,<br>4. ACS,<br>5. Post stroke,<br>6. Type 2 DM+ post ACS,<br>7. T2D + stroke, post ACS + post stroke, | Top 3 drivers:<br>1. proportion of patients on diet and exercise who revert from prediabetes to normal glucose tolerance following treatment<br>2. the proportion of patients on liraglutide who |

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| | | | | | 8. Post ACS + post stroke,<br>9. T2D + post ACS + post stroke,<br>10. death.<br><br>Scenario analysis:<br>11. Cancer<br>12. T2DM+Cancer | revert from prediabetes to normal glucose tolerance<br>3. weight reduction at the start of year 2 with diet and exercise.<br><br>• Assumptions of cardiovascular outcome benefits that were based on temporary improvements in risk factors. |
| TA875 (NICE 2023), UK | • BMI ≥ 30 kg/m2 patients with at least one weight- | Semaglutide | (1) diet and exercise | Markov cohort model, 1-year, 40 years, healthcare | 11 health states<br>1. Normal glucose tolerance, | Top 3 drivers:<br>1. the starting BMI of the cohort |

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| | related comorbidity (base case)<br>• BMI ≥35 kg/m2, non-diabetic hyperglycaemia, high risk for CVD | | alone; (2) liraglutide | perspective and social services perspective | 2. non-diabetic hyperglycaemia,<br>3. non-diabetic hyperglycaemia reversal,<br>4. Type 2 DM,<br>5. ACS,<br>6. Post stroke,<br>7. Type 2 DM+ post ACS,<br>8. T2D + stroke, post ACS + post stroke,<br>9. Post ACS + post stroke,<br>10. T2D + post ACS + post stroke,<br>11. death. | 2. the discount rate for QALYs<br>3. the weight reduction at the start of Year-2 with diet and physical activity.<br><br>• Assumption uncertainties, the rebound in weight gain after semaglutide is stopped. |
| TA1026 (NICE 2024), UK | • BMI ≥30 kg/m2 with at least one | Tirzepatide | diet and exercise | Microsimulation (both being a | 10 health states | • Assumptions regarding the |

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| | weight-related comorbidity (base case)<br>• BMI ≥35 kg/m2 with at least one weight-related comorbidity<br>• BMI ≥35 kg/m2, non-diabetic hyperglycaemia, high risk for CVD. | | alone; semaglutide; (liraglutide as a comparator for a subgroup) | Markov model and an individual patient simulation), 4-week for the first 2 years followed by an annual cycle length for the rest of the lifetime time horizon, lifetime, healthcare perspective and social services perspective | 1. Normal glucose tolerance,<br>2. Pre-DM<br>3. Temporary reversal Pre-DM<br>4. stroke,<br>5. MI,<br>6. angina,<br>7. sleep apnoea,<br>8. NAFLD,<br>9. T2DM<br>10. death. | HbA1c values of simulated patients for normoglycaemia and prediabetes, cost offsets and quality of life gains from avoiding T2DM. |
| NG246 (NICE 2025), UK | • People with DM and overweight (BMI>25 kg/m2)/obesity (BMI>30 kg/m2) | Diet interventions | usual care (conventional diet and standard | Multi-cohort Markov model, 1 year, lifetime, healthcare perspective and | health (alive), diseases, dead (all causes), dead (disease). | Driver: benefits of weight reduction on diabetes remission. |

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| | • Mixed population with overweight (BMI>25 kg/m2)/ obesity (BMI>30 kg/m2) (including with and without DM) | | weight management) | social services perspective | 8 independent Markov models to project the lifetime incidence of diabetes, IHD, stroke, selected cancers, and cirrhosis. | |
| ICER 2022 (Atlas SJ et al. 2022), US | • Without pre-DM and either a BMI ≥30 kg/m2 or ≥27 kg/m2 with at least one weight-related comorbid condition (base-case)<br><br>• Adults were 80% female with an average age of 45 | • semaglutide<br>• liraglutide<br>• phentermine/ topiramate<br>• naltrexone/ bupropion | Standard lifestyle modification | Markov cohort model, 1-year, lifetime, healthcare perspective (Scenario Analyses with Societal perspective (including labour costs)) | <u>9 health states</u><br>1. No DM,<br>2. with DM,<br>3. MI,<br>4. stroke,<br>5. stroke+MI, or<br>6. other CVD,<br>7. HF,<br>8. Post-stroke+MI<br>9. death | Drivers:<br>health state utility, effectiveness of medication in reducing weight, and factors associated with prevention of diabetes mellitus, such as reduction in HbA1C with |

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| | yrs, BMI of 38 kg/m2 , SBP of 125 mmHg, and HbA1C of 5.7% without confirmed DM. (RCT+RWD); Scenario analysis with population consisting of men and women (50:50)<br><br>• Adults with a starting BMI of ≥40 kg/m2 (scenario analysis) | | | | | treatment and baseline HbA1C.<br><br>• Assumptions: Patients continue to receive the intervention or lifestyle modification throughout the model time horizon. Treatment discontinuation is included in the model prior to the first model cycle. longitudinal changes in the persistence and |

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| | | | | | | adherence to medications were not considered in the model.<br>Proportion of actively treated hypertension is a function of BMI without a significant influence on the incremental cost-effectiveness ratio,<br>In patients with hypertension, blood pressure is equally well managed across |

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| | | | | | | all weight loss treatments. |

**Tabe A2-2 Pharmacological treatments**

| Author, year, country setting | Population | Intervention | Comparator | Model type, cycle length, time horizon, Perspective | Health states | Model drivers/ key assumption or limitation |
|---|---|---|---|---|---|---|
| Kim 2022 (Kim et al. 2022), US | • Adults BMI ≥ 30 kg/m2<br>• Adults BMI 27-29.9, with at least one weight-related comorbidity | Semaglutide | Diet and exercise alone; and other anti-obesity medication (liraglutide, phentermine topiramate, and naltrexone bupropion). | Markov cohort model, 3 months was applied in the first year, annual cycles were applied after the first year. 30-year horizon, healthcare perspective | 10 health states<br>1. Normal glucose tolerance,<br>2. Pre-DM<br>3. Type 2 DM,<br>4. ACS,<br>5. Post stroke,<br>6. Type 2 DM+ post ACS, | Driver: maximum treatment duration and time horizon, followed by regimen after treatment discontinuation, weight-rebound rate, and semaglutide 2.4 mg efficacy on BMI. |

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| | | | | | 7. T2D + stroke, post ACS + post stroke,<br>8. Post ACS + post stroke,<br>9. T2D + post ACS + post stroke,<br>10. Death. | Assumptions:<br>• After AOM treatment discontinuation, weight loss benefit (represented by BMI reduction) is expected to diminish (ie, weight rebounds). The rebound rate was applied until patients' BMI returned to the baseline level.<br>• Patients discontinuing |

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| | | | | | | AOMs were assumed to continue lifestyle intervention until death or the end of the 30-year model. |
| McEwan 2025 (McEwan et al. 2025), US | Adults with obesity and cardiovascular disease without diabetes | Semaglutide | Diet and exercise alone | Markov cohort model, 4-week cycle; lifetime, healthcare perspective | 1. Established CVD (at baseline)<br>2. DM status<br>3. CKD stages<br>4. Non-CV death or CV death | Top 3 most influential inputs on maintenance cost: DM. Discontinuation rate as dose 24+ months. Costs discounting.<br><br>Top 3 most influential inputs on QALYs: Disutility BMI |

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| | | | | | | gain, benefits discounting, maintenance disutility: CKD stage 1. Cost-effectiveness outcomes were most sensitive to the following inputs: discounting of QALY benefits; the BMI-associated disutility; maintenance disutilities associated with CKD (particularly |

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| | | | | | | at early stages); and diabetes. |
| Rennert-May 2025 (Rennert-May et al. 2025), Canada | Adults with obesity and cardiovascular disease without diabetes | Semaglutide | Diet and exercise alone | Decision analytic Markov model, monthly cycle, 10-year (base case); Scenario: lifetime, healthcare perspective | 2 states<br>1. survive without complication, experience a health event<br>2. death | Driver: clinical effectiveness of semaglutide on mortality reduction and the cost of semaglutide.<br><br>• Assumption: mortality benefit conferred by semaglutide was attenuated. |
| Zomer 2024 (Zomer et al. 2024), Australia | Adults with obesity and cardiovascular disease without diabetes | Semaglutide | diet and exercise alone | Markov cohort, 1 year cycle, 20 year horizon, healthcare perspective | 3 states<br>1. Alive with CVD<br>2. Alive with recurrent CVD | Driver: cost of drug. |

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| | | | | | 3. Death | |
| Lumbreras 2023 (Lumbreras et al. 2023), US | Adults with a mean age of 45. Mean BMI of 37.1 for females and 36.8 for males (base case) | • semaglutide<br>• liraglutide<br>• tirzepatide<br>• phentermine/ topiramate<br>• naltrexone/bupropion | Diet and exercise alone | Decision analytic model, 1 year, 40 years horizon, healthcare perspective. | Treatment discontinuation;<br>Weight loss;<br>BMI categories;<br>CVD events and DM;<br>Death. | Driver: The model was more sensitive to the utility and cost of being obese (BMI≥30).<br><br>• Assumed life time therapy for those successful (patients experiencing at least 5% of body weight loss). |
| Alshahawey 2024 (Alshahawey et al. 2024), US | Adults with BMI ≥ 30 or ≥ 27 with one or more weight-related | Semaglutide | • liraglutide<br>• diet and exercise alone | Decision analytic model, 68 weeks horizon (17 months), | 1. Treatment continuation<br>2. Treatment success | |

| | | | | | | |
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| | comorbidities, without diabetes | | | healthcare perspective | 3. Achievement ≥15% weight loss | |
| Hu 2022 (Hu et al. 2022), China | Adult population with a BMI between 30.4 and 33.9 | • Liraglutide<br>• Semaglutide<br>• Dulaglutide<br>• Exenatide | No-treatment | Decision analytic model, 1 year horizon, healthcare perspective | | Driver: BMI loss parameter of Exenatide (treatment effectivness) and the costs of Semaglutide and Exenatide had a greater effect on the results than other parameters.<br><br>• Assumed the weight of untreated obese patients will |

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| | | | | | | continue to increase slightly over time. |
| Papantoniou 2025 (Papantoniou and Maniadakis 2025), Greece | Adults with BMI ≥ 30 or ≥ 27 with one or more weight-related comorbidities, without diabetes | Semaglutide | Liraglutide | Decision analytic model, 68 weeks horizon (17 months), healthcare perspective. | Thresholds:<br>1. achievement ≥5% weight loss<br>2. achievement ≥10% weight loss<br>3. achievement ≥15% weight loss<br>4. achievement ≥20% weight loss | Drivers:<br>1. the proportion of patients achieving the weight loss target with liraglutide<br>2. the ex-factory price of liraglutide<br><br>• Assumed maximum dosing per the trial protocol without accounting for real-world adherence. |

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| Mital 2023 (Mital and Nguyen 2023), US | Adolescents with severe obesity | • Orlistat<br>• Liraglutide<br>• Semaglutide<br>• Phentermine-topiramate<br><br>Sensitivity:<br>Metformin vs Bariatric surgery | No treatment | Microsimulation, 1 year cycle, 10 year horizon, healthcare perspective | 1. Adolescent healthy weight<br>2. Adolescent overweight<br>3. Adolescent obesity<br>4. Adolescent severe obesity<br>5. Adolescent healthy weight<br>6. Adolescent overweight<br>7. Adult obesity I<br>8. Adult obesity II<br>9. Adult obesity III<br>10. Death | Driver: most sensitive to drug costs and efficacy. |

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| Olivieri 2024 (Olivieri et al. 2024), Canada | Adult with BMI ≥ 30 kg/m2 or 27–30 kg/m2 and ≥1 weight-related condition, including T2D. | • Orlistat<br>• Liraglutide<br>• Semaglutide<br>• Naltrexone 32 mg/bupropion | Diet and exercise alone | Markov cohort, 1 year cycle, 40 years horizon, societal perspective | 11 health states:<br>1. Normal glucose tolerance,<br>2. non-diabetic hyperglycemia,<br>3. non-diabetic hyperglycaemia reversal,<br>4. Type 2 DM,<br>5. ACS,<br>6. Post stroke,<br>7. Type 2 DM+ post ACS,<br>8. T2D + stroke, post ACS + post stroke,<br>9. Post ACS + post stroke, | Non-responders to pharmacotherapy were assumed to discontinue treatment but continue lifelong diet and exercise (D&E) therapy, reflecting Canadian clinical guidelines where D&E is foundational and pharmacotherapy is continued only with meaningful weight loss after 3–6 months. |

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| | | | | | 10. T2D + post ACS + post stroke,<br>11. Death. | |
| Miguel 2024 (Miguel et al. 2024), Portugal | Adult with BMI≥30 kg/m2 with one or more obesity-related comorbidity | Semaglutide | Diet and exercise alone | Markov cohort, a 3-month cycle was used in the first year to better capture treatment effects and discontinuations. Annual cycles applied thereafter. 40 years horizon, healthcare perspective | <u>11 health states:</u><br>1. Normal glucose tolerance,<br>2. non-diabetic hyperglycemia,<br>3. non-diabetic hyperglycaemia reversal,<br>4. Type 2 DM,<br>5. ACS,<br>6. Post stroke,<br>7. Type 2 DM+ post ACS, | Drivers:<br>1. most sensitivity to variations in the discount rate applied to benefits.<br>2. the baseline incidence of post-menopausal endometrial cancer (for the non-obese Portuguese general population)/ |

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| | | | | | 8. T2D + stroke, post ACS + post stroke,<br>9. Post ACS + post stroke,<br>10. T2D + post ACS + post stroke,<br>11. Death. | 3. weight reductions applied in year 2 of the model on treatment with diet and exercise.<br><br>Treatment discontinuation was assumed for patients not responding to treatment. |

**Tabe A2-3 Non-Pharmacological treatments**

| Author, year, country setting | Population | Intervention | Comparator | Model type, cycle length, time horizon, Perspective | Health states | Model drivers/ key assumption or limitation |
|---|---|---|---|---|---|---|
| Bates 2022 (Bates et al. 2022), UK | • People with a BMI of 28kg/m2 or above without diabetes<br><br>• People with a diagnosis of T2DM prescribed one non-insulin diabetes medication. | Self-management interventions | No intervention | Microsimulation, 1-year, lifetime, healthcare perspective | | Duration of effect and the initial weight loss had the greatest impact on justifiable cost. |
| Arrospide 2022 (Arrospide et al. 2022), Spain | Spanish population | self-management interventions | No intervention | discrete event simulation model, lifetime, | | NR |

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| | | | | healthcare perspective | | |
| Avenell 2018 (Avenell et al. 2018), UK | Adult population with a BMI of ≥ 35 kg/m2 | (1) low intensity weight management<br>(2) Diet interventions<br>(3) Bariatric surgery | No intervention | Microsimulation, 1 year cycle, 30 years horizon, health and social perspective | 1. Health<br>2. One of the CVD events | Drivers: weight regain assumptions, time horizon, discount rate |
| Boyers 2021 (Boyers et al. 2021), UK | Adult with a BMI of ≥ 35 kg/m2 | (1) low-intensity weight management<br>(2) Diet interventions + weight management<br>(3) moderate intensit weight management | No intervention | Microsimulation, 1 year cycle, 30 years horizon, health and social perspective | 1. Health<br>2. One of the CVD events | Driver: assumptions about the rate of weight regain over time. |

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| | | (4) high intensity weight management<br>(5) Bariatric surgery | | | | |
| Galvain 2021 (Galvain et al. 2021), UK | • (1) adults with BMI 40 kg/m2, or BMI 35 kg/m2 with obesity-related comorbidities;<br>• (2) adults with BMI 35 kg/m2 with T2DM | Bariatric surgery | Self-management interventions | Markov cohort, I year cycle, lifetime, health and social perspective | 1. T2D<br>2. T2D remission<br>3. No TD2<br>4. Acute Stroke<br>5. MI<br>6. Cancer<br>7. Post stroke<br>8. Post MI<br>9. Death | NR |
| Gulliford 2017 (Gulliford et al. 2017), UK | Adults with BMI>40 kg/m2, including DM and other comorbidities | Bariatric surgery | Self-management interventions | Markov cohort, I year cycle, lifetime, health and social perspective | 1. At risk<br>2. DM<br>3. CHD<br>4. Stroke<br>5. Cancer | Driver: obesity-related physical and psychological comorbidities |

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| | | | | | 6. Death<br>Each state is stratified by BI category | were the main drivers of health-care costs. |
| Harrison 2021 (Harrison et al. 2021), UK | Adults with BMI > 35 kg/m2 | Bariatric surgery | Self-management interventions | Mendelian randomisation, health and social perspective | | N/A |
| Haseeb 2024 (Haseeb et al. 2024), US | Adult with BMI 35-39.9 kg/m2 | (1) Bariatric surgery<br>(2) Semaglutide | No treatment | Markov cohort, 1 month cycle, 5 year horizon, healthcare perspective | <u>For drug</u><br>1. Weight loss (year 1)<br>2. Weight loss/plateau<br>3. drop out<br><br><u>For surgery</u><br>1. Weight loss (year 1)<br>2. Weight loss/plateau | Driver: Annual drug cost of semaglutide, weight loss endoscopic sleeve gastroplasty (year 1), and drop-out rate of Semaglutide |

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| | | | | | 3. repeat procedure | Assumptions:<br>1. Assumed that patients who dropped out from the semaglutide strategy experienced weight loss for at least 3 months before starting to regain weight.<br>2. A proportion of patients with insufficient weight loss or weight regain underwent repeat surgery |

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| | | | | | | after the first year.<br>3. patients faced a 30-day mortality risk in our model based on expert opinion. |
| Kelly 2023 (Kelly et al. 2023), UK | Adults with BMI 35.0–39.9 kg/m2 | Bariatric surgery | Self-management interventions | Markov cohort, A cycle length of 6 months was used for the first year to reflect the immediate weight loss, and annual cycles were used thereafter, lifetime horizon, | <u>6 health states</u><br>1. Obesity III (BMI>40)<br>2. Obesity II BMI 35-39.9)<br>3. Obesity I (BMI 30-34.9)<br>4. overweight (BMI 25-34.9)<br>5. Healthy weight (BMI 18.5-24.9) | Drivers:<br>health state utility values and prevalence of type 2 diabetes in both the obesity I and II health states.<br><br>Assumptions: |

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| | | | | health and social perspective. | 6. Death | - Weight loss was assumed to plateau after 2 years (with BMI remaining constant thereafter) for 80% of model patients receiving ESG. To account for the potential of weight regain following ESG, the remaining 20% of patients receiving ESG were assumed to gradually |

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| | | | | | | return to baseline BMI by 5 years based on a recent systematic review and meta-analysis of studies assessing weight regain following bariatric surgery. Explored in sensitivity analysis with more conservative assumption. |

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| | | | | | | - Co-morbidity associated disutility assumed to be accounted for in BMI based health state utility values.<br>- 100% compliance with lifestyle modification assumed. |
| Galekop 2024 (Galekop 2024), Denmark | Adults with overweight or obesity (BMI of 27 kg/m2 but < 40 kg/m2) and had no chronic diseases | Personalised Nutrition Plan | General Nutrition Plan | Markov cohort, 1 year, lifetime, societal perspective | <u>10 health states</u><br>1. No DM/ No IHD/ no Stroke<br>2. IHD<br>3. DM<br>4. Stroke<br>5. DM+IHD | Driver: the effect in HRQoL (short-term trial effect) had the most impact. |

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| | (e.g., diabetes and cancer) | | | | 6. IHD+Stoke<br>7. DM+ Stroke<br>9. DM+IHD+Stroke<br>10. Death | |

**A3: Risk equations used in TAs**

| **Liraglutide TA664**<br>Risk equation used and sources (123 of 196) | | | |
|---|---|---|---|
| **Complication** | **Risk equation(s) available in model** | **Justification for base case selection** | **Committee and Evidence Review Group (ERG) Discussion** |
| Risk of type 2 diabetes onset in normal glucose tolerance (NGT) patients | QDiabetes-2018 Model C (UK) | The QDiabetes risk model was preferred as being the most validated risk score in a UK population, allowing 10 years prediction of risk including prediction of risk in patients with prediabetes (122). | The committee accepted the use of risk equations in the model but was concerned about assuming long-term cardiovascular benefits from temporary improvements in risk factors. However, clinical experts clarified that short-term weight loss and diabetic status improvements from liraglutide could reduce long-term risks of myocardial infarction, angina, and stroke. |
| Risk of type 2 diabetes onset in patients with prediabetes | • QDiabetes-2018 Model C (UK) adjusted to reflect a higher risk of diabetes by setting the HbA1c parameter equal 42 mmol/mol (6 %- points) then held constant over time until diabetes development.<br>• *Alternative: Framingham Offspring Study adjusted to reflect a higher risk of diabetes by setting the FG 100-126 mg/dL parameter equal to 1 (parameter is 0 for normal glucose tolerance patients) | | |

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| Risk of CVD in primary prevention in NGT and prediabetic patients | • QRisk3 (UK)<br>• *Framingham Heart Study | The QRisk3 equation was used to predict the risk of first cardiovascular event in prediabetes and normal glucose tolerance states and was chosen because it contains UK cohort and as such is being used in UK. | |
| Risk of CVD in secondary prevention in NGT patients | Framingham Recurrent Coronary Heart Disease (US) | The Framingham Recurring Coronary Heart Disease risk model was used to predict recurrent cardiovascular events. | |
| Risk of CVD in primary prevention in patients with type 2 diabetes | • UKPDS82 (UK)<br>• *Alternative 1: QRisk3<br>• *Alternative 2: Swedish NDR | The UKPDS 82 risk model (outcome model 2) was used, as it is a UK study and able to predict both | |

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| | | first and recurrent cardiovascular events after the onset of type 2 diabetes. | |
| Risk of CVD in secondary prevention in patients with type 2 diabetes | • UKPDS82 (UK)<br>• *Alternative: Framingham Recurrent Coronary Heart Disease (US) | The UKPDS 82 risk model (outcome model 2) was used, as it is a UK study and able to predict both first and recurrent cardiovascular events after the onset of type 2 diabetes . | |
| Risk of knee replacement | Incidence in reference BMI group and per unit increase from calculated. | Did not provide | |
| Obstructive sleep apnoea prevalence | Prevalence by BMI level from the Sleep Heart Study. | Did not provide | |
| Risk of colorectal cancer | • Incidence in reference BMI group: US National Institutes of Health (NIH) AARP Diet and Health Study | Meta-analyses and systematic review were | |

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| | • Risk adjustment by BMI level: Meta-analysis: Schlesinger, S., Lieb, W., Koch, M., Fedirko, V., Dahm, C.C., Pischon, T., Nöthlings, U., Boeing, H. and Aleksandrova, K., 2015. Body weight gain and risk of colorectal cancer: a systematic review and meta-analysis of observational studies. Obesity Reviews, 16(7), pp.607-619.<br>• Alternative: Incidence in reference BMI group AND risk adjustment by BMI: US National Institutes of Health (NIH) AARP Diet and Health Study: Adams et al. Body mass and colorectal cancer risk in the NIH-AARP cohort. Am J Epidemiol. 2007 Jul 1;166(1):36-45. | preferred over individual studies. | |
| Risk of endometrial cancer in post-menopausal women | Incidence in the reference BMI group and per unit BMI increase calculated from: Renehan et al. Body mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. | | |

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| | The Lancet, 2008; 371(9612), pp.569-578<br><br>*Alternative: Million Women Study: Yang TY, Cairns BJ, Allen N, Sweetland S, Reeves GK, Beral V; Million Women Study, Post-menopausal endometrial cancer risk and body size in early life and middle age: prospective cohort study, Br J Cancer. 2012 Jun 26;107(1):169-75. | | |
| Risk of breast cancer in post-menopausal women | Incidence in the reference BMI group and per unit increase calculated from: Renehan et al. Body mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. The Lancet, 2008; 371(9612), pp.569-578 | Meta-analyses and systematic review were preferred over individual studies. | |

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| | *Alternative: Ahn J, Schatzkin A, Lacey JV Jr, Albanes D, Ballard-Barbash R, Adams KF, Kipnis V, Mouw T, Hollenbeck AR, Leitzmann MF Adiposity, adult weight change, and post-menopausal breast cancer risk Arch Intern Med. 2007 Oct 22;167(19):2091-102. '- Study conducted on 99,039 post-menopausal women in the US National Institutes of Health–AARP Diet and Health Study | | |

NGT: normal glucose tolerance; CVD: cardiovascular disease

Note: *Scenario analysis

| **Semaglutide TA875**<br>Risk equations used for obesity-related complications (116 of 176) | | | |
|---|---|---|---|
| **Complication** | **Risk equation(s) available in model** | **Justification for base case selection** | **Committee and ERG Discussion** |

| | | | |
|---|---|---|---|
| Onset of T2D | • QDiabetes-2018 Model C<br>• Framingham Offspring* | QDiabetes allows prediction of 10-year risk and includes BMI and HbA1c as predictive variables. This is in line with assumptions from TA664. | • The committee expressed concern that the risk equations used to model long-term cardiovascular and diabetes outcomes were based on surrogate markers and lacked validation in populations without diabetes, especially for cardiovascular benefits. They also noted that these equations assume a steady state and may not accurately reflect the time-limited effects of semaglutide, making it difficult to quantify long-term benefits reliably. *(see 3.16)*.<br>• The committee noted that excluding cardiovascular benefits from the model had only a small upward effect on the ICER, while excluding diabetes-related benefits had a larger impact, significantly increasing the ICER. This suggests that although the reliability of risk equations was a concern, particularly for cardiovascular outcomes, the model remained cost-effective even without those benefits, with diabetes outcomes being more |
| First CV event | • Qrisk3<br>• Framingham Heart Study* | The QRisk3 contains a UK cohort and as such is being used in UK. This is in line with assumptions from TA664. | |
| Recurrent CV event | • Framingham Recurring Coronary Heart Disease | The only risk equation identified for recurrent CV events in non-diabetic patients. This is in line with assumptions from TA664. | |
| First CV event in T2D | • UKPDS82<br>• Qrisk3* | The UKPDS 82 risk model (outcome model 2) is a large UK study and able to predict both first and recurrent CV events after the onset of T2D. This is in line with assumptions from TA664. | |
| Incidence of recurrent CV event in T2D | • UKPDS82<br>• Framingham Recurring Coronary Heart Disease* | | |
| Onset of OSA | Sleep Heart Study | This study preferred to other available studies because it was the | |

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| | | largest in sample size (n=5,615), it provided sufficient data to calculate a prevalence rate per unit BMI, and it investigated the prevalence of moderate-to-severe OSA (AHI ≥15), given that in the present health-economic analysis, OSA was assigned a hospital cost for continuous positive airway pressure treatment. | influential in determining cost-effectiveness. |
| Knee replacement | Wendelboe et al. 2003 | The study provided granular data on the association between BMI and incidence of knee surgeries by 2.5 BMI-unit steps for observed BMI levels between 17.50 and 42.49 kg/m2 . | |

Note: *Scenario analysis to test assumptions regarding choice of risk equation on CE

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Risk equation used and sources (178 of 258)

| Population | Complication | Risk equation(s) available in model | Base case source in previous TAs | Justification for base case selection | Committee and EAG Discussion |
|---|---|---|---|---|---|
| Patients without T2DM | Development of T2DM | • Base case: QDiabetes<br>• Scenario: Framingham Offspring Study | TA875 and TA664: aligned | In addition to being aligned with both TA875 and TA664, this source was considered more suitable for use in the base case as it has been externally validated, had a larger patient cohort than the Framingham Offspring Study and has been widely used in the UK, given this study was conducted in England | • The committee was concerned that using risk equations based on surrogate outcomes like BMI to predict long-term clinical events introduced uncertainty, as these estimates were not supported by direct trial evidence. Additionally, the model excluded relevant baseline comorbidities and outcomes such as cancer, which may be influenced by BMI, potentially |

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| | | | | (whereas the Framingham Heart Study was based in the US). | undermining the accuracy of treatment benefit estimates.<br>• The committee was concerned that annualising multi-year risk estimates could lead to events being predicted too early and too frequently, introducing bias in the model. This compounding effect may overestimate event incidence, especially in the active treatment arms, although scenario analyses showed it had limited impact on cost-effectiveness estimates. |
| | CVD (stroke, MI and angina): Initial | • Base case: QRisk3<br>• Scenario: Framingham Heart Study | TA875 and TA664: aligned | Similarly to the QDiabetes risk equations for T2DM, the use of the QRISK3 risk equation in the base case is aligned with both TA875 and TA664 and this source has been externally validated, had a larger patient cohort than the Framingham Heart Study and has been widely used in the UK since this study was conducted in England | |

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| | | | | (whereas the Framingham Heart Study was based in the US). | |
| | CVD (stroke, MI and angina): Recurrent | • Base case: Framingham Heart Study<br>• Scenario: LIPID Study | TA875 and TA664: aligned | This risk equation was chosen for the base case as it is considered robust and is widely used. This risk equation also explicitly considers the increased risk of recurrent CVD events among patients who have already experienced a CVD event. It also included a larger patient cohort compared with the LIPID study, and has previously been used | |

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| | | | | and accepted in prior TAs for obesity. Although it was developed specifically in a US context, no suitable alternative in a UK context were identified. | |
| Patients with T2DM | CVD (stroke, MI and angina): Initial<br>CVD (stroke, MI and angina): Recurrent | • UKPDS82 | TA875 and TA664: aligned | This risk equation was chosen for the base case since it explicitly considers the increased risk of recurrent CVD events among patients who have already experienced a CVD event. It has also been externally validated, is widely used in the UK | |

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|---|---|---|---|---|---|
| | | | | and is aligned with both TA875 and TA664. | |
| All patients | Knee replacement | Wendelboe et al. 2003 | TA875 and TA664: aligned | This study was chosen as no appropriate alternative risk equations were identified. It was also used in the base case of the models presented in TA664 and TA875, and Company evidence submission template for tirzepatide for managing overweight and obesity [ID6179] © Eli Lilly and Company (2023). All rights reserved Page 178 of 258 was deemed | |

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| | | | | appropriate by the Committee in these appraisals. | |
| | OSA | Erridge et al. 2021 | TA875 and TA664: Young et al. 2002 (Sleep Heart Study) (not aligned) | Erridge et al, 2021 is a UK study which included 276,600 patients with obesity (BMI ≥30 kg/m2 ) identified during a data extraction of the CPRD in 2017, with median follow up of 147.0 months. This source was preferred compared to the study used in TA664 and TA875 (Young et al. 2002) due to its larger sample size, UK population, recency, | |

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| | | | | and the granularity of the BMI covariate, in particular between 30 and 40 BMI kg/m2 where the majority of the patient population is expected to be upon entering the model. | |
| | NAFLD | Loomis et al. 2016 | N/A – not included in previous appraisals (and noted by the Committee in TA875 as an omission of benefit) | The incidence rate for patients in the model developing NAFLD are based on a study by Loomis et al. 2016, a retrospective population-based longitudinal cohort study conducted using The Health Improvement Network (THIN) database in the | |

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| | | | | UK. Loomis et al. fitted Cox proportional hazard models to a cohort of 1,133,525 patients (followed up for a median of 4.96 years) to derive hazard ratios (HRs) based on BMI category, sex and diabetes status. The patient data used were collected between 2007 and 2013. Although no internal or external validation was conducted to assess the discrimination or calibration of the models, no suitable | |

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| | | | | alternative sources were identified. | |