DISCRETE EVENT SIMULATION IN OBESITY: A FEASIBILITY STUDY

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What was known

- Obesity is a highly prevalent health condition [1] with severe sequalae and complications [2,3] that result in impaired health-related quality of life [4] and considerable cost burden [2]
- Several new pharmaceuticals for treatment of obesity have been assessed by NICE; while patient population in routine care is heterogenous with complex interactions between risk-factors, cost-effectiveness analyses have relied on markov cohort models [5-7]
- Discrete event simulation has been utilised in other chronic disease areas [8] and just recently in obesity [9] to model heterogenous patient populations and complex interactions of risk-factors that determine long-term outcomes

What's new

- A patient-level discrete event simulation (DES) framework has been developed for the obesity indication to address heterogeneity in the patient population and to allow modelling sub-groups through distinct risk-factor profiles
- This research demonstrates general feasibility of DES in obesity and in particular for cost-effectiveness assessment with sub-group and sensitivity analysis for NICE technology appraisal

Background

In the UK, most adults, 67% of men and 60% of women, are overweight or suffer from obesity, and 26% of men and 29% of women suffer from obesity [1]. Obesity is associated with multiple complications and increased mortality [2,3] and spending on overweight and obesity-related ill-health is expected to reach £9.7 billion by 2050 in the UK National Health Service (NHS) [5].

Health economic models to assess cost-effectiveness have utilised Markov cohort approaches that classify obesity mainly by body mass index (BMI) and type-2 diabetes mellitus (T2DM) status to model complication rates, costs, and utilities [6-8]. To account for heterogeneity in the patient population and complex interdependencies between risk-factors new patient-level health economic models in obesity are needed to assess cost-effectiveness and impact on long-term outcomes, especially for stratified and/or sub-group specific approaches.

Objective

The objective of this study was to assess the feasibility of developing a probabilistic discrete event simulation (DES) in obesity for technology appraisal (TA) by the National Institute for Health and Care Excellence (NICE) and to validate the model results against results from past NICE TAs and published models.

Methods

A systematic literature review of published cost-effectiveness modelling was performed to inform model concept. To supplement cost-effectiveness studies from pre-2015 identified in a published systematic review [10], a systematic search of electronic databases (MEDLINE, Embase, the Cochrane Library and EconLit) was conducted from 1 May 2015 to 24 August 2020. A total of 15 cost-effectiveness models were identified to extract relevant disease states and model events. The model diagram is outlined in Figure 1.

A patient-level simulation model was implemented in the R software package [11] using time-to-event calculations with a lifetime horizon and discounting of 3.5% for costs and utilities as per the NICE reference case [12]. The discrete event simulation (DES) approach was chosen to account for heterogeneity in the modelled patient population and to link continuous variables to outcomes through risk equations.

Natural history of BMI trajectories was estimated based on equations from a UK study that analyzed 100,000 patients from the UK general practice research database [13]. Two predictive equations were defined, relating BMI to age and sex for diabetic and non-diabetic cohorts.

Risk-equations

For patients entering the model without type-2 diabetes mellitus (T2DM) the Qdiabetes-2018 risk model was used to estimate time to onset of T2DM [14]. T2DM-related complications (e.g. amputation, blindness, ESRD, ulcer) were modelled using the UKPDS 82 risk equations [15].

The Qrisk3 risk model was used to estimate the risk of primary CV events [16]. For secondary CV events, the risk was estimated using the Framingham Recurring Coronary Heart Disease Risk Model [17]. CVD events were simulated as composite events due to lack of granularity in the risk equations for predicting these events individually (MI, angina, stroke, TIA). CVD events were then disaggregated into their individual components based on a predefined distribution [17,18].

Other clinical events modelled included e.g., onset of hypertension, osteoarthritis, obstructive sleep apnea and colorectal cancer. A full list of clinical events and risk equations used to model time to event is outlined in Table 1.

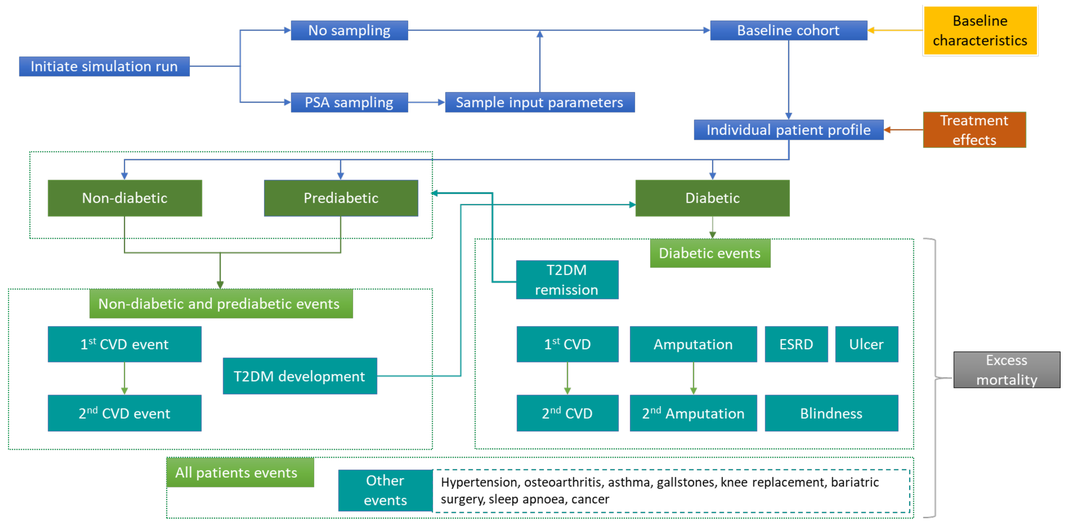
Mortality

All-cause mortality for patients without T2DM was accounted for in the model based on UK life-tables. All-cause mortality associated with T2DM was included based on UKPDS equations [15]. Further, event-specific mortality was modelled using equations and published hazard ratios that estimate the excess risk of mortality associated with an event i.e., case fatality rates (acute mortality) and HRs of excess mortality (post-acute mortality).

Cost

Obesity management cost related to the patient's BMI was derived from a study by Wang et al. [19]. Any costs associated with major diagnostic code categories of events accounted for by the model directly were removed to avoid double-counting. The BMI-specific cost represents any direct medical costs that are not accounted for in the estimation of acute and long-term event costs, such as general prescription and obesity related visit costs. Event costs were derived from published literature identified during systematic literature review.

Figure 1. Model diagram for discrete event simulation in obesity



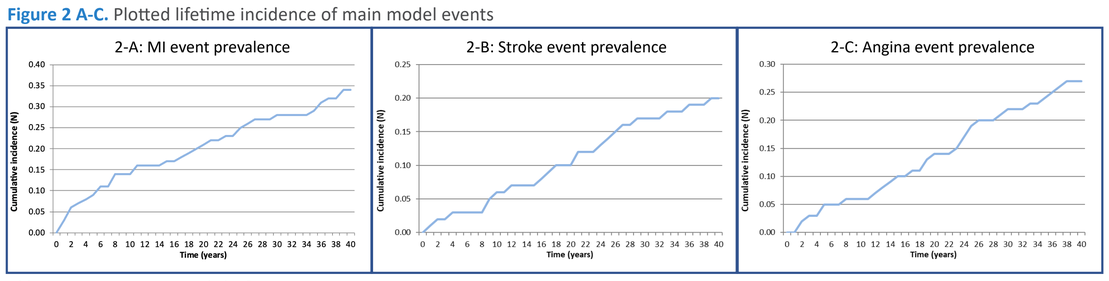
Abbreviations: CVD – cardiovascular disease, T2DM type-2 diabetes mellitus

Table 1. Summary of model events and risk equations

Obesity-related event	Description of risk/hazard model	Source
Onset of T2DM	Qdiabetes-2018 risk model	[14]
Onset of first CV event	Qrisk3 risk model	[16]
Onset of second CV event	Framingham Recurrent Coronary Heart Disease risk model	[17]
T2DM complications	UKPDS82 risk model	[15]
T2DM remission	HbA1C <6.5% threshold	[20]
Hypertension	Risk model derived from the Third National Health and Nutrition Examination Survey, the Framingham Heart Study and other sources	[21]
Osteoarthritis	Hazard ratios for knee and hip replacement relating to osteoarthritis and BMI	[22]
Asthma	Risk model derived from the Norwegian Prescription Database and health surveys	[23]
Gallstones	Risk model derived from US Health Professionals Follow-up Study and the Nurses' Health Study	[24]
Knee replacement	Risk model based on odds rations reported by Wendelboe et al.	[25]
Colorectal cancer	Risk model derived from US National Institutes of Health AARP Diet and Health Study	[26]
Breast and endometrial cancer	Risk model based on regression analysis from systematic literature review	[27]
Onset of OSA	Prevalence by BMI level derived from the Sleep Heart Study	[28]

Abbreviations: BMI = body mass index, CKD = chronic kidney disease, CV = cardiovascular, ESRD = end-stage renal disease, HbA1C = glycated haemoglobin, OSA = obstructive sleep apnoea, T2DM = type-2 diabetes mellitus

Figure 2 A-C. Plotted lifetime incidence of main model events



Abbreviations: MI – myocardial infarction

Figure 3 A-B. Comparison of total costs and QUALYs

Abbreviations: COM – Core Obesity Model, QUALY – quality adjusted life-year, TA – technology appraisal
Sources: NICE 2017 [5], NICE 2020 [6] and data on file

Methods continued

Health-related quality of life

Patients were assigned a baseline utility based on age at entry to the model. Baseline utilities were obtained from the Department of Health's Health Survey for England [29]. Utility gain or loss related to weight loss or gain, respectively, was derived from a regression analysis of the relationship between BMI and health utility [4] and implemented in the model accordingly.

Incidence of clinical events predicted within the model is associated with reductions in health-related quality of life (HRQL). Disutility was defined by two model inputs. The first disutility value is applied during the year of the event and represents acute impairment of HRQL. The second disutility value is applied in subsequent years and represents chronic impairment of HRQL. Data for the first and second disutility were derived from systematic literature review.

Results

100 patients were simulated for base case feasibility analysis of routine care management with diet and exercise in obesity. Model events included e.g., onset of T2D, sleep apnea, cardiovascular disease, knee replacement and all-cause mortality. Lifetime incidence and costs per patient of main clinical events are outlined in Table 2. Plotted lifetime incidence of the three most common clinical events (MI, stroke and angina) is depicted in Figure 2 A-C.

Modelled QALYs amounted to 16.055 and were comparable with published results from TA 664 (QALYs: 15.216) and TA 494 (QALYs: 15.134). Modelled total costs per patient amounted to £27,600 per patient and were in the range of TA664 (£19,780) [6] but higher than estimates from TA494 (£6,502) [5]. A comparative summary of model outcomes is depicted in Figure 3 A-B.

Incidence and costs of main clinical events over patient lifetime were comparable with those of the Core Obesity Model (COM) [30]. Lifetime incidence and costs per patient of main clinical events of this DES and the COM is outlined in Table 2.

Table 2. Lifetime incidence and cost of modelled clinical events vs. COM, per patient

Event	Incidence		Total cost	
	DES model	COM	DES model	COM
MI	0.34	0.22	£25,509	£14,511
Stroke	0.20	0.16	£4,980	£4,272
Angina	0.27	0.28	£4,737	£5,921
Colorectal cancer	0.07	NA	£3,657	NA
Incident diabetes	0.04	NA	£521	NA

Abbreviations: COM – Core Obesity Model, DES – discrete event simulation, MI – myocardial infarction

Conclusions

Probabilistic DES in obesity is feasible with the R software package. Model runtime for 100 patients was less than 1 minute and the described modelling approach will allow running large cohorts with sensitivity analysis and acceptable runtime for NICE TA.

A key difference between this model and previously published obesity models is the use of updated, recent risk equations, consideration of additional clinical events and use of latest cost data. This explains differences in incidence and cost outcomes between this DES and previously published cohort model.

In addition, observed differences in costs and QUALYs between obesity models are due to inclusion of different sets of clinical events considered in the respective models. The model described herein follows the precedence to including the most prevalent and impactful events (such as MI, stroke and T2DM), while also exploring the impact of events that tend to be under-reported in obesity models (such as microvascular events and cancer). With this approach additional events were directly included in the simulation rather than inflating BMI-related overhead cost for general management costs of obesity to account for events not modelled explicitly.

Considering the results from this feasibility analysis, simulating larger cohorts, fully validating results according to ISPOR standards [31] and benchmarking economic outcomes against data from published models, clinical trials and real-world evidence databases is warranted.

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Disclosures

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