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REVIEW

Critical Analysis of Markov Modeling for the Economic Evaluation of Obesity Interventions: A Systematic Review

Qiucen Lin[1], Carolina Oi Lam Ung[1–3], Yunfeng Lai[4], Hao Hu[1–3], Mihajlo Jakovljevic[5–7]

[1]State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao, People's Republic of China; [2]Centre for Pharmaceutical Regulatory Sciences, University of Macau, Macao, People's Republic of China; [3]Department of Public Health and Medicinal Administration, Faculty of Health Sciences, University of Macau, Macao, People's Republic of China; [4]School of Public Health and Management, Guangzhou University of Chinese Medicine, Guangzhou, People's Republic of China; [5]UNESCO-TWAS, The World Academy of Sciences, Trieste, 34100, Italy; [6]Shaanxi University of Technology, Hanzhong, 723099, People's Republic of China; [7]Department of Global Health Economics and Policy, University of Kragujevac, Kragujevac, Serbia

Correspondence: Hao Hu; Mihajlo Jakovljevic, Email haohu@um.edu.mo; sidartagothama@gmail.com

Background: Obesity poses significant health and economic burdens globally, with interventions requiring robust cost-effectiveness evaluations. Markov models are widely utilized in economic evaluation of obesity interventions, their structure, assumptions, and related uncertainties have not yet been thoroughly evaluated.

Objective: This study aimed to systematically review the Markov models used for the economic evaluation of anti-obesity interventions, describe their structural characteristics, identify key uncertainties, and provide insights for future research.

Methods: The review was conducted across three databases (PubMed, Embase, the Cochrane Library) and health technology assessment agency websites to identify published Markov model-based full economic evaluations in adults with obesity from their inception to 2 June 2024. Model structure, model uncertainty, and validation were extracted from the included studies. Philips checklist for the methodology quality of modeling studies was performed.

Results: The review included 21 primary publications with 21 unique Markov models. Two modeling approaches regarding the progression of obesity and its impact were identified: direct BMI to cost and utility; and BMI-linked complications, with diabetes and cardiovascular diseases most frequently modeled. Validation practices were inconsistently reported (43% of models), and structural uncertainty (eg, BMI trajectory assumptions) was rarely addressed. Quality assessment revealed moderate rigor (a mean compliance rate of 78% across all criteria), with gaps in transparency and generalizability, particularly for non-Western populations. Probabilistic sensitivity analysis was universal, yet scenario analyses highlighted outcome sensitivity to complication inclusion and time horizons.

Conclusion: While Markov models are commonly utilized in obesity intervention evaluations, methodological heterogeneity and insufficient validation limit comparability and reliability. Future models should prioritize standardized validation (eg, ISPOR guidelines), broader complication spectrum, and diverse population data. Enhancing transparency in structural assumptions and uncertainty analysis is critical for robust policy recommendations.

Keywords: obesity, Markov model, disease progression, economic evaluation

Introduction

Obesity is a complex, progressive, chronic disease characterized by excessive accumulation of body fat that impairs health and is associated with an increased risk of premature morbidity and mortality.[1–3] Historically, obesity was rare and associated with affluence in traditional societies, and its global prevalence has more than doubled since 1990, affecting 16% of adults globally in 2022.[2,4,5] Notably, substantial increase of obesity was seen among lower- and middle-income countries, which might be driven by reduced physical labor due to technological advancements, urbanization, and reliance on affordable, calorie-dense processed foods.[6–10] Recent advances in obesity management include GLP-1 receptor agonists (eg, semaglutide) and dual GLP-1/GIP agonists like tirzepatide, which promote weight loss and

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metabolic improvements.[11] Nevertheless, bariatric surgery has proven to be more effective superior in facilitating weight loss and addressing overall metabolic imbalances for eligible patients, such as those with severe obesity and comorbidities.[12]

Regarding the scarce healthcare resources and the potentially high cost of such interventions, economic evaluations are increasingly performed to inform decisions by comparatively analyzing their cost and consequence.[13] The decision analytic model has increased prominence in economic evaluation, especially for cases like obesity, a chronic relapsing progressive disease process. A review by Bjoern Schwander et al provided a comprehensive overview of published decision models for health economic assessments related to obesity, various methodological approaches were identified and Markov models dominated (85% of studies).[14] Similarly, a review of 23 bariatric surgery cost-effectiveness studies reported 70% used state-transition models, including 10 Markov models.[15] Cohort-based Markov approaches were also prevalent in pharmacoeconomic evaluations of anti-obesity medications.[16]

Markov model is particularly well-suited for modeling chronic diseases, in which a hypothetical cohort of individuals resides in a finite number of mutually exclusive health states at every point in time, all transition probabilities are constant or depend only on calendar time (ie, time in model).[17,18] It enables analysis of long-term outcomes, time-dependent intervention, and population-level strategies while maintaining transparency and simplicity for decision maker. Moreover, Markov model is relatively simple to develop, debug, communicate, and analyze using user-friendly software.[19]

Despite the widespread use of Markov models in economic evaluation of obesity interventions, their structure, assumptions, and related uncertainties have not yet been thoroughly evaluated. Therefore, this study aimed to systematically review the Markov models used for the economic evaluation of obesity interventions, describe their structural characteristics, identify key uncertainties, and provide insights for future research.

Methods

Search Strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20] A search strategy was devised using each database's specified set of search terms (Supplementary Table S1). In brief, the search was designed to identify published economic modeling studies in adults with obesity. Searches were performed in PubMed, Embase, and the Cochrane Library on 2 June 2024, with no start date restrictions, ensuring coverage of all relevant studies from database inception to the search date. The bibliographies of eligible articles were reviewed to identify any additional relevant publications that could be included in the review.

Additionally, we also searched the websites of the following health technology assessment agencies (HTA): the UK National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Institute for Clinical and Economic Review (ICER).

Literature Selection

Identified records were downloaded and screened for inclusion based on the predefined inclusion and exclusion criteria (Supplementary Table S2): briefly, only Markov model-based full economic evaluations (including cost-effectiveness, cost-utility, and cost-benefit studies) of anti-obesity interventions in adults with obesity would be included.

Downloaded literature was selected in steps. Firstly, duplicates were removed, and irrelevant records were excluded based on the eligibility criteria during title and abstract screening. Secondly, full-text publications were obtained for the remaining citations, and the screening process was repeated using the eligibility criteria for full-text articles to obtain a final set of included publications. For models described in multiple publications, the most comprehensive journal article (preferred over Health Technology Assessment report) would be included as the primary source for this study, while the remaining publications as secondary sources. The screening process was conducted by two reviewers independently, and any disagreements were resolved through further discussion or by consensus with a third reviewer.

Data Extraction and Analysis

Data extraction was performed using a pre-designed data extraction form. One reviewer performed data extraction, which was checked by two reviewers independently. The following data were extracted from the included studies: (1) General study characteristics, including authors, year of publication, country, intervention, target population, funding sources, conflicts of interest, health outcomes, perspective, and time horizon of analysis; (2) Model characteristics, including graphical representation, health states, cycle length, software used, calibration of parameters, model validation, and types of sensitivity analysis.

Quality Assessment

Quality assessment was performed using the Philips Checklist.[21] Philips checklist was a 57-item checklist to evaluate the methodological quality of modeling studies across three dimensions: structure, data, and consistency, as recommended by the National Institute for Health and Care Excellence (NICE).[22] Two reviewers assessed the quality of the included studies independently, and any disagreements were resolved through further discussion or by consensus with a third reviewer.

Results

Literature Search Results

We followed PRISMA guidelines (Supplementary Table S3), the flow diagram (Figure 1) outlines study selection. The search yielded 3,561 hits via database search, of which 869 were excluded after removing auto-duplicates (Figure 1). Further 2,562 hits were excluded based on title and abstract screening. We sought to obtain the full text of the remaining 130 hits, and 38 hits with abstract only were excluded. Full publications of 92 hits were assessed, and 30 studies that met our criteria were included. We also searched the websites of HTA agencies; 8 health technology assessment (HTA) reports were identified, and 4 reports were included in the review after full-text screening. As such, a total of 34 studies were identified.

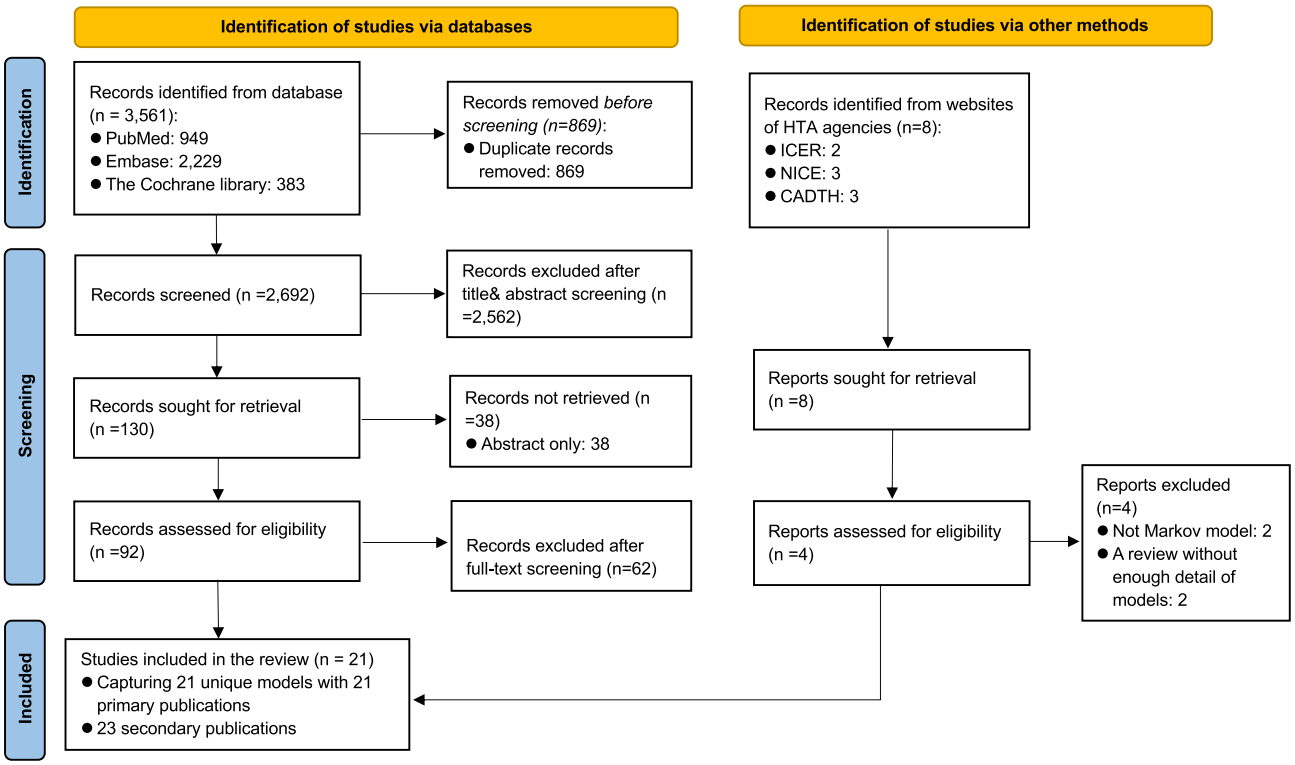

Figure 1 PRISMA flowchart of the study selection process.

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Following a detailed review of these 34 publications, 21 unique models with 21 primary publications were included in the current review,[23–43] and the remaining 23 publications were documented as secondary sources (Supplementary Table S4). The most frequently applied model was the model by Borisenko O et al, used in seven publications to assess the cost-effectiveness of bariatric surgery in different countries.[30] This was followed by the Core Obesity Model (COM),[44,45] employed in four publications to evaluate the cost-effectiveness of anti-obesity medications (AOMs). Fifteen other models were described in only one publication.[24,25,28,29,31–35,37–42]

General Study Characteristics

The main characteristics of the 21 identified Markov-based economic evaluations are summarized in Table 1.

Regarding time horizon, most included studies applied a lifetime horizon[23–25,27–30,32,34–36,39,41,42] or a relatively long-time horizon (ie, 40 years or 30 years).[37,40,43] Two studies chose a 20-year time horizon to assess the cost-effectiveness of surgery.[26,38] In the Health Technology Assessment issued by the Institute for Clinical and Economic Review (ICER) in 2015, an 11-year time horizon was applied: a one-year time horizon to assess the immediate clinical and economic effects of bariatric surgery, a newer medication, and a newer type of device, and a cost-utility analysis was also conducted over a ten-year time horizon based on assumed trajectories of BMI change after the various surgical, pharmacological, and device interventions.[31] A shorter time horizon – 5 years, was applied by Gil-Rojas et al, considered clinically relevant and owing to available efficacy data.[33] For the cycle length, all Markov models utilized annual cycles with one exception utilized 1-month cycle length.[30]

All economic evaluations of obesity interventions have been conducted in western countries, except two studies focusing on Colombia and South Korea seperately.[27,33] Most of the studies (52%, 11/21) were funded and sponsored by the industry,[24,28–30,33,35–38,41,42] 24% (5/21) by government,[23,25–27,42] 10% (2/21) by the nonprofit organization,[31,39] and 14% (3/21) without funding.[32,34,40]

Apart from cost/LYs/QALYs/ICER, other model outcomes were also considered in the studies reviewed, such as the cumulative incidence of events,[28,39,42] and the absolute risk and relative risk of events.[30]

Among the studies that reported the use of software (n = 15), half of the studies (8/15) used Microsoft Excel (Microsoft Corporation),[23,29–31,37,38,41,43] whereas TreeAge (TreeAge Software, Inc.) was used by six studies.[27,28,32,33,35,40] One study used software developed by Simul 8 (Simul8 Corporation).[25]

Model Structure

A model structure is designed to describe the relevant clinical pathways for patients undergoing treatment with the interventions under evaluation. This structure is informed by both the characteristics of the interventions themselves and the established understanding of the natural history of the specific condition in question.[18] Additionally, the model structure incorporates insights into how these interventions may influence the progression of the condition. Hence, the natural history of the condition is very important in designing a Markov model given that the model is structured around health states, contributing to our understanding of the disease. The transition probabilities between these health states determine disease progression and must align with current knowledge of the natural history of obesity to ensure their relevance for evaluation purposes.

A total of twenty-one unique Markov models were included in our review, with substantial variations being observed across the studies, as shown in Table 2. A clear graphical representation of the model structure was provided in most studies, except for two.[24,31] The number of health states included in the Markov models ranged from 4 to 19.

There were two main approaches to modeling the impact of obesity and anti-obesity intervention on cost and health consequence: (1) direct BMI to cost and consequence; (2) BMI change to obesity-related complications.

A much more straightforward approach, BMI change transferred into cost and consequences directly, was employed by four models to assess the cost-effectiveness of bariatric surgery.[24,31,32,34] In these models, the natural history of obesity was reproduced and governed by the transition between various BMI categories, eg, not obese (BMI < 30 kg/m^2); obese (BMI 30–34.9 kg/m^2); morbidly obese I (BMI 35–39.9 kg/m^2); morbidly obese II (BMI40-49.9 kg/m^2); and super obese (BMI > 50 kg/m^2) and death.[24]

Table 1 Main Characteristics of the Markov-Based Modelling Studies

Author, Year	Country	Population	Interventions vs Comparators	Time Horizon	Cycle Length	Model Outcomes	Sponsor	Software
Galani C et al 2007[23]	Switzerland	Overweight or obesity	Lifestyle intervention vs standard care	Lifetime	1-year	Cost; LYs; QALYs; ICER	Government	Microsoft Excel
Campbell J et al 2010[24]	US	BMI > 40 or BMI > 35 with comorbid conditions	Bariatric surgery vs no treatment	Lifetime	1-year	Cost; LYs; QALYs; ICER	Industry	Not reported
Ara et al 2012[25]	UK	Obesity with or without DM	Pharmacotherapy vs placebo	Lifetime	1-year	Cost; LYs; QALYs; ICER	Government	Simul8
Picot J et al 2012[26]	UK	Mild (BMI: 30 to 34.99) or moderate (BMI: 35 to 39.99) obesity	Bariatric surgery vs non-surgical treatment	20-year	1-year	Cost; QALYs; ICER	Government	Not reported
Song HJ et al 2013[27]	South Korea	Morbid obesity (BMI ≥ 35), or obesity (BMI: 30–34.9) with obesity-related comorbidities.	Bariatric surgery vs non-surgical treatment	Lifetime	1-year	Cost; QALYs; ICER	Government	TreeAge Pro
Fuller NR et al 2014[28]	Australia	Overweight, obesity or DM	Commercial program vs standard care	Lifetime	1-year	Cost; LYs; QALYs; ICER; cumulative incidences	Industry	TreeAge Pro
Meads DM et al 2014[29]	UK	Overweight or obesity	Commercial program vs standard care	Lifetime	1-year	Cost; QALYs; ICER	Industry	Microsoft Excel
Borisenko O et al 2015[30]	Sweden	Obesity with or without DM	Bariatric surgery vs conservative management	Lifetime	1-month	Cost; QALYs; ICER; absolute risk and relative risk	Industry	Microsoft Excel
ICER 2015[31]	US	Obesity	Surgical-, device-, and medication-based treatments vs conventional weight-loss management	11-year	1-year	Cost; QALYs; ICER	Nonprofit organization	Microsoft Excel
James R et al 2017[32]	Australia	Obesity	Bariatric surgery vs usual care	Lifetime	1-year	Cost; QALYs; ICER	Unfunded	TreeAge Pro
Gil-Rojas Y et al 2019[33]	Colombia	Obesity with one of the following comorbidities: diabetes mellitus type 2, hypertension, dyslipidemia, or sleep apnea.	Bariatric surgery vs nonsurgical treatment	5-year	1-year	Cost; QALYs; ICER	Industry	TreeAge Pro

(*Continued*)

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Table 1 (Continued).

Author, Year	Country	Population	Interventions vs Comparators	Time Horizon	Cycle Length	Model Outcomes	Sponsor	Software
Mital S, Nguyen HV 2019[34]	US	Obesity	Aspiration Therapy, bariatric Surgery vs No treatment	Lifetime	1-year	Cost; QALYs; ICER	Unfunded	Not reported
Rognoni C et al 2020[35]	Italy	Obesity	Bariatric surgery vs diet	Lifetime	1-year	Cost; QALYs; net monetary benefit	Industry	TreeAge Pro
Galvain T et al 2021[36]	UK	Obesity with or without DM	Bariatric surgery vs non-surgical treatment	Lifetime	1-year	Cost; LYs; QALYs; ICER	Industry	Not reported
Kim et al 2022[37]	US	Obesity or overweight with ≥ one obesity-related comorbidities	Pharmacotherapy vs D&E, no treatment	30-year	1-year	Cost; LYs; QALYs; ICER	Industry	Microsoft Excel
Walter E et al 2022[38]	Australia	Obesity	Bariatric surgery vs non-surgical treatment	20-year	1-year	Cost; LYs; QALYs; ICER	Industry	Microsoft Excel
ICER 2022[39]	US	Obesity without DM	Pharmacotherapy vs lifestyle modification	Lifetime	1-year	Cost; LYs; QALYs; evLY; cumulative incidence and overall survival	Nonprofit organization	Not reported
Gómez Lumbreras A et al 2023[40]	US	Obesity without comorbidities	Among different pharmacotherapy	40-year	1-year	Cost; QALYs; ICER	Unfunded	TreeAge Pro
Kelly J et al 2023[41]	UK	Obesity	Bariatric surgery vs lifestyle modification	Lifetime	1-year	Cost; QALYs; ICER	Industry	Microsoft Excel
Galekop MMJ et al 2024[42]	Denmark	Overweight or obesity	Personalized nutrition plan vs control management	Lifetime	1-year	Cost; LYs; QALYs; cumulative incidence	Government	Not reported
Olivieri AV et al 2024[43]	Canada	Obesity or overweight with ≥ one obesity-related comorbidities	Pharmacotherapy vs D&E	40-year	1-year	Cost; QALYs; ICER	Industry	Microsoft Excel

Abbreviations: D&E, diet and exercise; evLY, equal-value life year; Lys, life years; QALYs, quality-adjusted life years; UK, the United Kingdom; US, the United States.

Table 2 Summary of Model Structure

Author, Year	Graphically Represented	Health States				
		States Number	BMI-Categories	Obesity-Complications		
				DM	CVD	Others
Galani C et al 2007[23]	Yes	7	Not reported	DM	Stroke and CHD.	Hypertension, hypercholesterolemia.
Campbell J et al 2010[24]	NR	6	Not obese; obese; morbidly obese I; morbidly obese II; and super obese.	Not reported	Not reported	Not reported
Ara et al 2012[25]	Yes	13	Not reported	Y	MI and stroke.	Not reported
Picot J et al 2012[26]	Yes	6	Not reported	DM and remission of DM.	CHD [acute myocardial infarction (AMI)] and stroke.	Not reported
Song HJ et al 2013[27]	Yes	5	Not reported	DM (Embedded in mild/ moderate comorbidity)	Coronary artery disease and/or stroke (Embedded in severe comorbidity)	Hypertension, dyslipidemia (Embedded in mild/ moderate comorbidity)
Fuller NR et al 2014[28]	Yes	7	Normal BMI, overweight BMI, obese BMI.	T2D	Not reported	Not reported
Meads DM et al 2014[29]	Yes	9	No included as health state.	T2D	Stroke and MI.	Not reported
Borisenko O et al 2015[30]	Yes	14 for surgical arm	Not reported	DM and remission of DM.	Peripheral artery disease, stroke, post-stroke, angina, post MI, HF, transient ischemic attack.	Absence of initial surgery, conversion surgery, and surgical complications states included in surgical arm
ICER 2015[31]	Unclear for the Markov process	Not reported	Change of BMI but not specific.	DM (captured via BMI change)	Not reported	Hypertension resolution, apnea resolution, hyperlipidemia resolution (captured via BMI)
James R et al 2017[32]	Yes	6	Normal weight, overweight, obesity class I, obesity class II, and obesity class III.	Not reported	Not reported	Not reported
Gil-Rojas Y et al 2019[33]	Yes	5 for each subgroup	Not reported	DM and DM remission in DM subgroup	AMI and stroke	Hypertension, dyslipidemia, or sleep apnea and their remission for each of the comorbidity's subgroup
Mital S, Nguyen HV. 2019[34]	Yes	5	Not obese, obese 1, obese 2, obese 3.	Not reported	Not reported	Not reported
Rognoni C et al 2020[35]	Yes	12	Not reported	DM, DM remission	Stroke, MI.	Complications of diabetes including amputation, nephropathy, retinopathy, hypoglycemic events, hyperglycemic events; Colorectal cancer

(*Continued*)

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Table 2 (Continued).

Author, Year	Graphically Represented	Health States				
		States Number	BMI-Categories	Obesity-Complications		
				DM	CVD	Others
Galvain T et al 2021[36]	Yes	19	Not reported	No DM, DM, DM remission.	Stroke and MI	Cancer (based on meta-analyses of all cancer types, rather than a specific cancer type)
Kim et al 2022[37]	Yes	18	Not reported	DM	Acute coronary syndrome [ACS, (includes MI and unstable angina)] and stroke.	Postmenopausal endometrial, postmenopausal breast, and colorectal cancer
Walter E et al 2022[38]	Yes	16	Not reported	DM and its complications as a whole; no DM.	CVD (including angina, HF, hypertensive heart disease), no CVD, stroke, post-stroke, MI, post-MI.	Hyperlipidemia, no hyperlipidemia, depression, no depression, NASH, no NASH.
ICER 2022[39]	Yes	15	Not reported	DM	MI, stroke, HF, and other CVD (including peripheral artery disease, angina, and transient ischemic attack).	Not reported
Gómez LA et al 2023[40]	Yes	4	BMI < 25; BMI 25–29; BMI ≥ 30.	DM, embedded in each BMI-related health state)	HF, CHD, stroke. Embedded in each BMI-related health state	Not reported
Kelly J et al 2023[41]	Yes	6	Healthy weight, overweight, obesity I, obesity II, and obesity III	T2D, Embedded in each BMI-related health state)	Not reported	Hypertension, sleep apnoea, gastro-oesophageal reflux disease, non-alcoholic fatty liver disease
Galekop MMJ et al 2024[42]	Yes	9	Not reported	DM	IHD and stroke.	Not reported
Olivieri AV et al 2024[43]	Yes	18	Not reported	DM	ACS, (includes MI and unstable angina)] and stroke.	Postmenopausal endometrial, postmenopausal breast, and colorectal cancer

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index, kg/m^2; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IHD, ischemic heart disease; MI, myocardial infarction; NR, not reported; T2D, type 2 diabetes.

Various BMI categories were utilized as distinct health states within the model; patients transition between Markov states by changing BMI (losing or gaining weight) or dying. Each of these health states was assigned specific cost and utilities. A critical distinction emerged in the methodologies used to assign BMI-specific healthcare costs and health-related quality-of-life (HRQoL) utilities across studies. In two studies, costs and utilities were systematically derived for each BMI category using direct evidence from published sources, such as healthcare expenditures and quality-of-life values specific to BMI categories.[24,34] In contrast, two other studies adopted a linear extrapolation method to estimate BMI-related changes in costs and utilities.[31,32] Baseline costs and utilities for each health state were extracted from available data, while BMI change-related costs and utilities were estimated via linear extrapolation. Commonly, this approach assumed uniform gains (eg, consistent utility improvements per unit of BMI reduction) to model outcomes.

The other distinct method, change in BMI transferred into the incidence of obesity-related complications that subsequently impact the cost and consequences, stood out as the most widely adopted.[23,25–30,33,35–43] In these models, the natural history of obesity was simulated, reflecting the transitions between obesity, obesity-related complications, and death.

Commonly, BMI change was modeled continuously, then the incidence of obesity-related complications and mortality were estimated based on the BMI change with incorporation of additional related risk parameters when appropriate. Nevertheless, three models involved using various BMI categories to define health states in the preceding setting, and BMI categories-related complications were modeled as distinct health states[29,40] or implicitly included.[41]

Regarding the obesity-related complications considered, diabetes mellitus (DM, 15/15) was the most frequently modeled, followed by cardiovascular disease (CVD, 14/15). However, there was notable heterogeneity among the different models in their consideration of DM and CVD.

Most models considered DM alone, while DM-related complications were included as distinct health states in two models as well.[35,38] Five models included patients with DM at baseline, explicitly modeling DM remission as a potential benefit of bariatric surgery.[26,30,33,35,36]

In the modeling of CVD, stroke was the most frequently modeled, followed by myocardial infarction (MI). Secondary CVD event was also considered by three models.[25,29,43]

Of note, the more recently developed models appear to incorporate a broader range of complications compared to previous models.[35–38,43] Among them, cancer was the most frequently considered. However, there was significant heterogeneity among the studies, with one study encompassing all cancer types collectively,[36] while others focused on specific types of cancer often encompassing various cancer types within these categories.[35,39,43] Additionally, as evidence increasingly highlights the association between BMI, sleep apnea, and knee replacement surgery, three models incorporated the impacts of these conditions, although outside the Markov framework.[36,37,43] Furthermore, depression and nonalcoholic steatohepatitis (NASH) were also included in the analysis by Walter E et al.[38]

In the context of obesity-related complication simulation, a diverse array of approaches was identified. Two studies applied country-specific databases to estimate the relationship between BMI and related complications.[25,27] For the other studies, relationships from the published studies are applied. When simulating diabetes mellitus, the most widely adopted approach was BMI-dependent risk estimation via polynomial regression, as proposed by Picot J et al.[46] It was used by four models. For cardiovascular disease (CVD), the dominant strategy involved applying the Framingham Heart Study risk equation. [26,30,35,36,39,43] This equation estimates overall 10-year CVD risk by integrating key clinical predictors, including age, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, smoking status, and diabetes status.[47] However, in Markov models focused on obesity, nuanced approaches were employed to account for heterogeneous CVD outcomes, such as myocardial infarction (MI), stroke, and heart failure. This allowed for a more granular estimation of CVD-related morbidity and mortality tied to BMI trajectories.

Model Uncertainty

All models included were able to deal with model uncertainty, which was described in varying levels of detail in the primary publications (Table 3). All included studies conducted probabilistic sensitive analysis (PSA). Deterministic sensitive analysis (DSA) was reported in most studies considering diversity variables, except two.[23,35] Among the studies

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Table 3 Uncertainty and Validation

Author, Year	Uncertainty			Validation
	DSA/Most Influential Parameters	PSA	Scenario Analysis	
Galani C et al 2007[23]	Not reported.	Yes	Not reported.	Not reported.
Campbell J et al 2010, US[24]	Yes. Cost-related.	Yes	Y. Using alternative estimates of efficacy data.	Not reported.
Ara et al 2012[25]	Yes. The baseline BMI for the cohort	Yes	Not reported	Not reported.
Picot J et al 2012[26]	Yes. Changes in utility gains from BMI reduction, surgeon performance, and diabetes management costs. Result for 2-,5-year time horizon reported, when the time horizon increases, the ICER becomes lower	Yes	Not reported	Face validity, cross validity
Song HJ et al 2013[27]	Yes. Time horizon and discount rate.	Yes	Not reported.	Face validity, cross validity
Fuller NR et al 2014[28]	Yes. The costs associated with patient travel.	Yes	Yes. When the program costs of the CP in Australia were reduced to the equivalent of the Weight Watchers NHS referral scheme, our base case results were strengthened, and the CP remained the dominant intervention.	Not reported.
Meads DM et al 2014[29]	Yes. Robust to a number of DSA.	Yes	Yes. Still indicated dominance in favor of the commercial program.	Not reported.
Borisenko O et al 2015[30]	Yes. (1) the magnitude of the effect of surgery, (2) start age, (3) BMI (better to operate patients when BMI is lower), and (4) inclusion of an annual visit to a surgeon during the follow-up program from year three and onwards. The most sensitive parameter from cost variables was the annual cost of type 2 diabetes.	Yes	Yes. An additional 11 scenario analysis showed that uncertainty around the model inputs and structure did not affect the main results significantly.	Face validity, internal validity, and external validation.
Daniel AO et al 2015[31]	Yes. Time horizon, the cost of bariatric surgery.	Yes	Yes. A best case scenario and a worst case scenario.	Not reported.
James R et al 2017[32]	Yes. The health state costs, surgery cost, efficacy of surgery, and discount rate.	Yes	Yes. Varying the initial health state (obesity classification)	Not reported.
Gil-Rojas Y et al 2019[33]	Yes. Discount rate in some health condition of the patient cohort.	Yes	Not reported.	Face validity
Mital S, Nguyen HV. 2019[34]	Yes. Weight loss effects, discontinuation rates	Yes	Not reported	Not reported.
Rognoni C et al 2020[35]	Not reported.	Yes	Yes. Different perspective considered.	Face validity

Galvain T et al 2021[36]	Yes. BMI-related inputs, such as disutility per unit increase in BMI	Yes	Yes	Not reported.
Kim et al 2022[37]	Yes. Maximum treatment duration and time horizon, regimen after treatment discontinuation, weight-rebound rate, and semaglutide 2.4 mg efficacy on BMI.	Yes	Yes.	Face validity, cross validity, internal validity, external validation.
Walter E et al 2022[38]	Yes. Diabetic medication costs, mean percentage of weight change, surgery costs, diabetic complication costs, and QALY weights	Yes	Not reported.	Not reported.
ICER 2022[39]	Yes. The disutility per BMI change, effectiveness of each treatment in weight loss, baseline HbA1C, and cost of diabetes mellitus	Yes	Yes. Most influential factors: drug pricing (branded vs generic); perspective of analysis (societal vs health care sector); drug X (hypothetical agent, with better efficacy). Moderate Impact Factors: demographic adjustments (gender, BMI); complication inclusion- potential impact of cancer or chronic kidney disease.	Face validity, internal validity, cross validity, and external validation.
Gómez LA et al 2023[40]	Yes. The utility and cost of being obese (BMI Z > 30), price of some AOMs, and cost of stroke and diabetes.	Yes	Not reported.	Face validity, internal validity, and cross validity.
Kelly J et al 2023[41]	Yes. The health state utility values and prevalence of type 2 diabetes in both the obesity I and II health states.	Yes	Yes	Face validity
Galekop MMJ et al 2024[42]	Yes. The intervention costs, the effect of the intervention on BMI, the duration of the QoL effect, and the short-term effect of the intervention on utility.	Yes	Yes	External validation, cross validation reported elsewhere.[48]
Olivieri AV et al 2024[43]	Yes. Different set of baseline cohort characteristics; a faster catch-up rate post-treatment; discounting rates applied to benefit when versus next best alternative /treatment durations when versus the current standard care	Yes	Yes. If the modeled weight-loss benefits on cancer, mortality, CV, or osteoarthritis surgeries are excluded simultaneously, orlistat emerges as the best value for money alternative compared to current standard care.	Face validity, internal validity, cross validity, and external validation were performed in the Core Obesity Model.[44,45]

Abbreviations: DSA, deterministic sensitive analysis; PSA, probabilistic sensitive analysis.

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DSA performed, the most frequently reported influential factors were the utility associated with BMI change,[26,36,39–41] the cost of Type 2 diabetes (T2D) management,[26,30,38–40] and time horizon.[26,27,31,37,42]

Additionally, scenario analyses were performed in most studies. In the study of Borisenko O et al, 11 scenario analysis showed that uncertainty around the model inputs and structure did not affect the main results significantly.[30] However, the study of Olivieri AV et al found that when the weight-loss benefit on cancer, mortality, cardiovascular disease or osteoarthritis surgeries were excluded simultaneously, orlistat emerged as the best value for the money alternative compared to the current standard care.[43] Scenario analysis was also performed in ICER-2022, with the most influential factors including drug price, perspective of analysis, and a hypothetical drug agent with better efficacy; and the moderate impact factors including demographic adjustments, complication inclusion for the potential impact of cancer or chronic kidney disease.[39]

Model Validation

Model validation is a crucial process that assesses whether a model accurately represents the system it aims to simulate, involving various methods such as face validity (wherein experts evaluate model structure, data sources, assumptions, and results), verification or internal validity (check accuracy of coding), cross validity (comparison of results with other models analyzing the same problem), external validity (comparing model results with real-world results), and predictive validity (comparing model results with prospectively observed events).[49]

Among the twenty-one unique models, various methods of validation were reported in nine models (43%),[26,30,33,37,39–43] and only a small proportion of studies reported internal and external validation processes (Table 3). One model reported conducting internal validity by use of alternative data on complication risks, use of microsimulation analysis instead of Markov cohort analysis, and use of life years as an outcome.[34] The study by Galekop MMJ et al,[42] which was developed as part of the COMPAR-EU project to estimate the (cost-)effectiveness of self-management interventions for obesity and included partners from five different countries (Germany, Greece, the Netherlands, Spain and the UK) was a part of COMPAR-EU project, the external validity and cross validity was reported elsewhere.[48]

A comprehensive three-step validation process was employed by the model of Borisenko O.[30] First, the face validity of modelling results was assessed. Second, numerous "stress tests" were performed to verify the technical performance of the model. Third, an external validation of the model was performed using three large epidemiological studies (ASCOT-BPLA,[50] AHEAD[51] and ACCORD[52]) and the Scandinavian Obesity Surgery Registry annual report-2011.

The Core Obesity Model was well developed and has undergone thorough validation, with the details of its development and validation process published.[44,45] As reported, for most outcomes, the predictions of the COM showed good linear correlation with observed outcomes, as evidenced by the high coefficients of determination (R^2 values). The independent validation revealed a degree of underestimation in predictions of cardiovascular (CV) disease and mortality, and type 2 diabetes.

The model developed by ICER for their obesity management report in 2022 was also well-validated and comprehensively reported in their HTA report.[39] When they changed their model inputs to resemble the study of Kim et al (ie, higher semaglutide unit cost, utility inputs, two-year treatment, and 30-year time horizon),[37] their incremental cost-effectiveness estimate comparing semaglutide to lifestyle modification approached their reported estimate comparing semaglutide to diet and exercise. The remaining difference in these incremental cost-effectiveness estimates could likely be explained by a much shorter 30-year life expectancy in all treatments reported in their model.

Quality Assessment

The results of quality assessment using the checklist by Philips et al[21] were presented in Figure 2 and Supplementary Table S5. Quality assessment revealed a mean compliance rate of 78% across all 57 checklist items, with unequal distribution both across studies and quality dimensions (model structure, data, consistency), indicating variability in methodological rigor and transparency. Notably, overall compliance with reporting checklist items improved in recent studies.[39,42,43] Meanwhile, quality assessment revealed that the included Markov models were well-suited for their

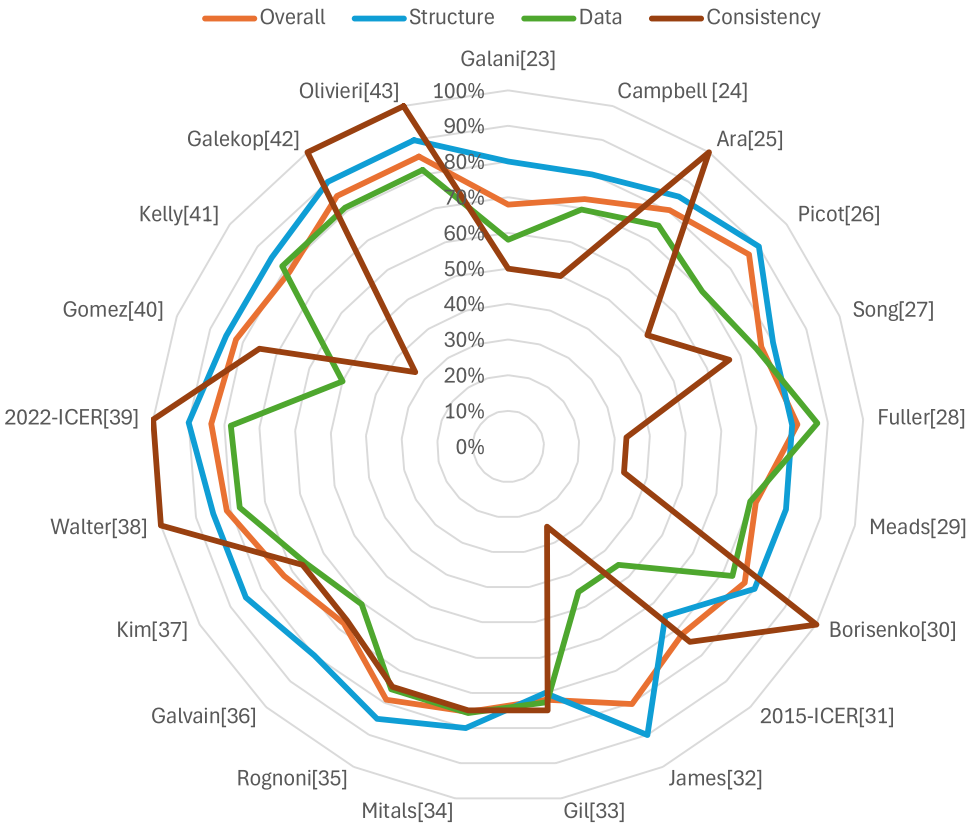

Figure 2 Proportion of adequately reporting the Philips checklist item.

purpose with a clear statement of decision problem and objective. The outcomes of all included models were consistent with their objective of the evaluation.

However, given that the models were predominantly intervention-specific, none of the included studies comprehensively evaluated all feasible and practical intervention options within their frameworks. Furthermore, the justification for excluding these viable alternatives was inadequately addressed, which might compromise the validity and generalizability of the findings. Though parameter uncertainty was frequently addressed via deterministic sensitivity analysis and probabilistic sensitivity analysis, few studies comprehensively addressed all of the four principal types of uncertainty—parameter, structural, heterogeneity, and methodological.[53]

Discussion

Principal Findings

Obesity presents rather unique and complex phenomenon in an array of other "prosperity" or noncommunicable diseases. It is also closely correlated with variety of diabetes, cardiovascular and cerebrovascular events, whose contribution to premature morbidity and preventable mortality remains huge.[54–57] Furthermore, specific opportunity cost of obesity is exceptionally high and widely related to the absenteeism and decreased or lost work ability. However, the complexity and costliness of these factors complicate precise quantification of both direct and indirect economic impacts.[58–61]

In the context of economic evaluations of anti-obesity interventions, Markov models have been widely applied to simulate the progression of obesity and its related health and economic outcomes. This systematic review identified 34 publications describing 21 unique Markov-based economic models evaluating obesity interventions, with 21 primary publications included. The included studies varied significantly in scope, methodological approaches, and reporting quality.

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Most models adopted a lifetime or long-term time horizon, reflecting the chronic nature of obesity. However, substantial heterogeneity in the modeling approaches across studies was identified. Two distinct approaches to modeling the progression of obesity and its impact on health outcomes have been observed. The first approach was relatively straightforward, directly translating the changes in body mass index (BMI) into associated costs and health consequences. Commonly, a linear extrapolation method to estimate BMI-related changes in costs and utilities was adopted. For example, a fixed utility gain or cost reduction was systematically applied, irrespective of baseline BMI or individual variability. This approach prioritized simplicity and generalizability but did not account for potential nonlinearities or threshold effects in BMI-related outcomes. It might oversimplify the progression of obesity and underestimate its associated cost and health consequences.

Interestingly, the study by Bjoern Schwander et al raises an important question: does the structure of a health economic model matter?[62] Their research found that in severely obese populations, the model's structure is crucial for accurately predicting clinical events. However, if the goal was simply to compare incremental health economic outcomes, the specific structure might be less significant, as the results tend to be comparable across different models. This suggests that while a well-structured model is essential for precise predictions, it may be less critical when evaluating cost-effectiveness in terms of incremental comparisons.

In contrast, the second and most widely adopted approach-BMI change modelled, and the change in BMI was transferred into the incidence of obesity-related complications that subsequently impact the cost and consequences. Obesity is recognized not only as a disease in its right but also as a significant risk factor for various chronic diseases, including cardiovascular disease, diabetes, and certain cancers[63–65] Consequently, when evaluating the impact of obesity and anti-obesity intervention on cost and health consequence, focusing solely on the impact of changes in body mass index (BMI) without considering the associated complications will likely lead to an underestimation of the true impact of obesity. This approach might better reflect the complex nature of obesity and its associated complications, acknowledging the intricate relationships between BMI, health outcomes, and economic implications.

There was considerable variability in the obesity-related complication addressed across the different models included in the analysis. For instance, the model developed by Fuller et al assessed only type 2 diabetes, as it was the sole condition for which baseline prevalence rates were available and because the link between BMI and type 2 diabetes is well established.[28] For studies only interested in diabetes mellitus as an outcome, this modeling approach would be suitable. However, for studies modeling interventions for people with obesity, other obesity-related complications would be relevant. As the authors noted, incorporating additional obesity-related diseases into the model would likely enhance the robustness of their existing conclusions.[28]

In line with this, the review revealed that among the models examined, diabetes mellitus and cardiovascular diseases, particularly MI and stroke, were the most frequently included obesity-related complications. This finding is consistent with the previous systematic review[14,66] and recommendations from an expert panel,[67] which suggested that models should incorporate at least three key comorbidities: coronary heart disease, type 2 diabetes, and stroke. According to a comprehensive report from the World Health Organization, there is substantial evidence—either strong or moderate—supporting the association of these conditions with obesity.[68] These conditions significantly affect health-related quality of life (HRQoL), life expectancy, and the utilization of healthcare resources and costs.[68,69] Furthermore, they are known to be influenced by weight management interventions.

Moreover, a broader range of obesity-related complications has been incorporated into the recently developed models. As reported by Olivieri AV et al, when the weight-loss benefit on cancer, mortality, cardiovascular disease or osteoarthritis surgeries was excluded simultaneously, orlistat emerged as the best value for the money alternative compared to the current standard care.[43] This finding underscores the necessity of comprehensively incorporating obesity-related complications in cost-effectiveness analyses to ensure accurate assessments of intervention value.

BMI categories were utilized in seven studies, with six focusing on the cost-effectiveness of bariatric surgery,[24,31,32,41] while one study concentrated on anti-obesity medications.[40] When evaluating the cost-effectiveness of anti-obesity medications using BMI categories approach, all treatments yielded similar quality-adjusted life years (QALYs).[40] The amount of weight loss with these medications was often insufficient to facilitate a transition from one BMI category to another, resulting in only modest differences in QALYs. In contrast, modeling BMI as a continuous

variable rather than categorically would enhance the model's flexibility in simulating the effects of interventions on BMI reductions.[48]

Regarding the relationship between BMI and obesity-related complications, the process of identifying studies reporting the association was often poorly described and rarely based on systematic or structured reviews. Moreover, existing Markov-based health economic models predominantly derived from Western populations—rely on data specific to Caucasian cohorts, which limits its generalizability to diverse ethnic or geographic groups. Introducing new data or calibrating existing risk equations could enhance the accuracy of decision-making in this context.[70]

With respect to the uncertainty, parameter uncertainty was consistently addressed via probabilistic sensitivity analysis (PSA) in most studies. Despite the critical importance underscored by established modeling guidelines, which necessitate the exploration of implications arising from alternative plausible assumptions,[71] structural uncertainty, particularly regarding assumptions about BMI trajectories, complication risks, and treatment effect durability, remains insufficiently addressed in current scholarly investigations. Addressing uncertainty in the model is not merely a technical step but a critical foundation for robust decision-making, substantial efforts must be devoted to systematically evaluating and mitigating it.

Validation practices were inconsistently reported and only a small proportion of studies reported internal or external validation processes. As trust and confidence are foundational to the success of health economic models, rigorous validation is imperative to ensure their reliability in informing policy and clinical decisions. There is an urgent need for concerted efforts to align validation practices with the 2012 ISPOR guidelines.[49]

Quality assessment of the 21 models was carried out by using the Philips checklist. Overall, the reviewed models achieved a mean proportion of 78% that adequately fulfilled across all criteria, indicating moderate methodological adequacy. However, stratified analysis revealed significant disparities between the structure section and data section, with models consistently more adequately reporting in structural design than in data handling and transparency. Most models failed to address structural uncertainty, such as assumptions about sustained treatment effects or its extrapolation methods, and omitted sensitivity analyses to test these assumptions. Furthermore, transparency gaps were evident in insufficient documentation of excluded interventions and incomplete consideration of uncertainty types (eg, parameter, structural, heterogeneity). These findings highlight critical limitations in methodological rigor, particularly the under-assessment of structural uncertainty and data-driven assumptions, which may undermine the reliability of cost-effectiveness conclusions in obesity intervention evaluations.

Limitations

This systematic review has several limitations that should be acknowledged. Firstly, the review was restricted to literature published in English, which may have resulted in the exclusion of relevant studies published in other languages, limiting the comprehensiveness of our findings. Secondly, the focus was solely on Markov models, excluding potentially valuable insights from non-Markov modeling approaches that could enhance understanding of the natural history of obesity and its related comorbidities. This focus may also lead to structural uncertainty, as variability in model assumptions and disease progression pathways can influence outcomes and cost-effectiveness conclusions. Thirdly, the Philips checklist,[21] a tool for evaluating the methodological quality of health economic models, exhibits limitations when applied to obesity-related studies. Many criteria assessments under this framework rely on subjective interpretations and lack specificity for modeling chronic, multifactorial conditions such as obesity. For instance, the checklist's generalized criteria may inadequately address the complexity of obesity dynamics, including long-term weight trajectories, behavioral heterogeneity, and interactions with comorbidities, thereby limiting its utility in ensuring methodological rigor for obesity-specific models.

Recommendations for Future Research

Future studies should prioritize enhancing methodological rigor in health economic models for obesity interventions by systematically addressing structural uncertainty through advanced sensitivity analyses, and adhering to standardized validation frameworks to ensure robust internal and external validation. Efforts must focus on improving transparency in data sourcing, justifying excluded interventions, and integrating diverse population data to enhance generalizability

across ethnic and geographic cohorts. Additionally, models should incorporate a broader spectrum of obesity-related complications using evidence synthesized from systematic reviews, while refining quality assessment tools to better capture chronic, complex disease dynamics. Calibrating risk equations to reflect non-linear BMI-outcome relationships and contextual factors (eg, socioeconomic disparities) will further strengthen the validity of cost-effectiveness conclusions.

Conclusion

This systematic review of Markov models in economic evaluation of obesity intervention underscores significant methodological heterogeneity, particularly in addressing structural uncertainty, validating assumptions, and generalizing findings beyond Western populations. Within Markov frameworks, the accuracy and reliability of modeling the impact of obesity and its interventions depend critically on methodological rigor, such as explicitly defined health states, the evidence-based transition probabilities, generalizable simulations of long-term outcomes, and comprehensive uncertainty analyses—particularly those addressing structural assumptions. Adherence to standardized validation frameworks (eg, ISPOR guidelines) is critical to ensure models reliably inform obesity-related reimbursement decisions. Future research should prioritize these frameworks alongside advanced uncertainty analyses and population-specific risk calibrations to strengthen cost-effectiveness evidence.

Data Sharing Statement

All the data has been included in the manuscript.

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Author Contributions

QCL, COLU, and HH conceptualized the study. QCL, COLU, and HH conducted the collection and analysis. All authors participated in the result interpretation. QCL drafted the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that they have no competing interests in this work.

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