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Cost-effectiveness of Semaglutide Compared With Other Glucose-Lowering Medications in Treating Type 2 Diabetes: A Comprehensive Systematic Review and Meta-analysis

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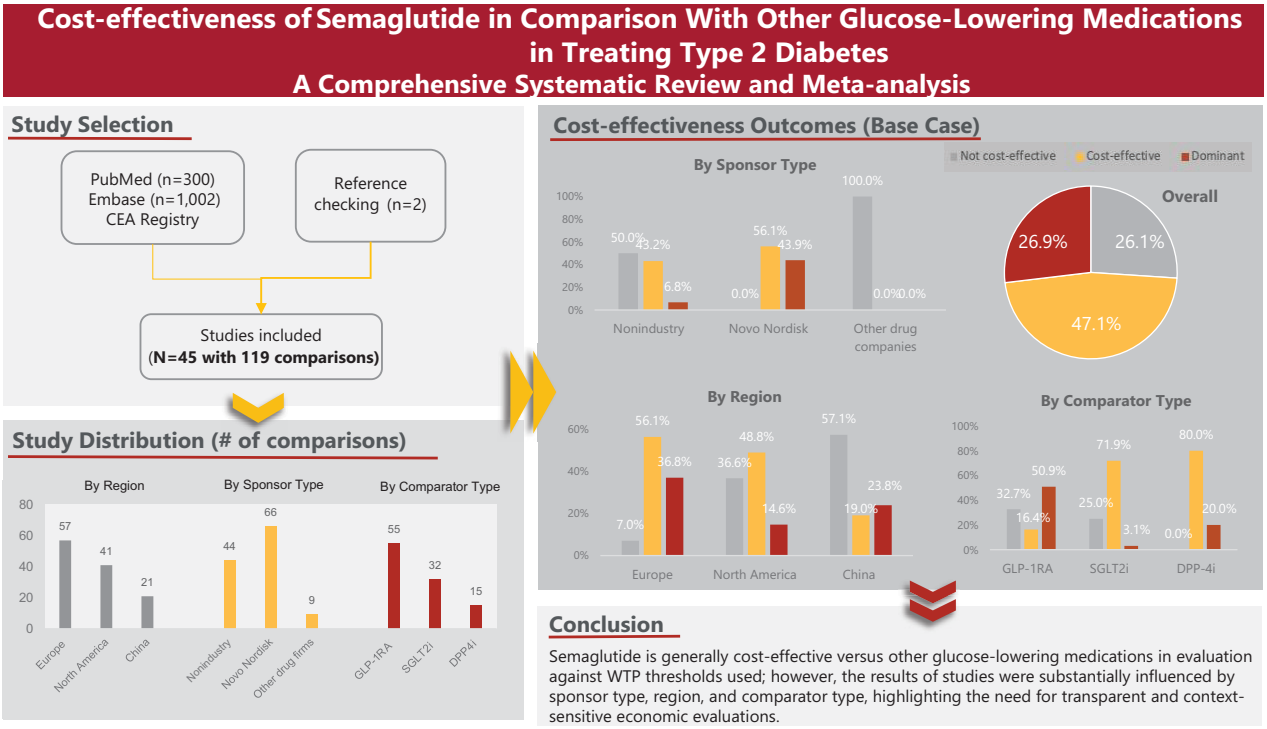

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  To address the need for updated evidence on cost-effectiveness of semaglutide and to fill existing evidence gaps by exploring the influence of region, study sponsor type, and model assumptions on findings on cost-effectiveness outcomes.

- **What is the specific question(s) we wanted to answer?**
  Is semaglutide cost-effective versus other medications for type 2 diabetes management? Are study results robust among different regions, study sponsor types, and model assumptions?

- **What did we find?**
  Semaglutide is generally cost-effective in comparison with other glucose-lowering medications, but results vary in considering study sponsor type, region, and model assumptions.

- **What are the implications of our findings?**
  The findings underscore the need for transparent, region-specific, and context-sensitive economic evaluations to inform evidence-based health care decision-making.

Cost-effectiveness of Semaglutide Compared With Other Glucose-Lowering Medications in Treating Type 2 Diabetes: A Comprehensive Systematic Review and Meta-analysis

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BACKGROUND

Significant clinical efficacy has been shown for semaglutide in managing type 2 diabetes (T2D); however, its cost-effectiveness remains uncertain.

PURPOSE

To systematically review existing evidence on cost-effectiveness of semaglutide versus other T2D medications.

DATA SOURCES

PubMed, Embase, and the Cost-Effectiveness Analysis Registry (by 11 June 2024).

STUDY SELECTION

A total of 45 articles (with 119 comparisons) from 2019 onward were included, representing Europe (*n* = 24), North America (*n* = 13), and Asia (all from China) (*n* = 8).

DATA EXTRACTION

Study characteristics and model characteristics/inputs/results were extracted. Lifetime costs and quality-adjusted life-years were evaluated. Proportions for cost-effectiveness outcomes (dominant, cost-effective, not cost-effective) were calculated. Subgroup analyses by region, sponsor type, comparator type, and model assumptions were performed. In sensitivity analysis a standard willingness-to-pay threshold was applied.

DATA SYNTHESIS

Of the articles included, 93.3% included adoption of a lifetime horizon and 84.4% a health care perspective and 68.9% were industry sponsored. For most studies reporting quality was high (86.7%). Overall, semaglutide was dominant/cost-effective in 73.9% of all comparisons. Notably, semaglutide was found to be dominant/cost-effective in all comparisons sponsored by Novo Nordisk versus in 50.0% of these funded by nonindustry sponsors and in none funded by other industry sponsors. Additionally, semaglutide was more cost-effective in high-income countries and in studies with adoption of a broader perspective, longer horizon, and lower discount rates. Results remained consistent with conversion with a common currency unit and willingness-to-pay threshold of US$50,000.

LIMITATIONS

Less detailed demographic information for more granular analyses.

SYSTEMATIC REVIEW

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CONCLUSIONS

Semaglutide is generally cost-effective compared with other glucose-lowering medications in evaluation against within-study willingness-to-pay thresholds; however, results varied by study sponsor type, region, and model assumptions, highlighting the need for transparent and context-sensitive economic evaluations.

The economic burden of type 2 diabetes (T2D) is substantial, with global health care expenditures increasing from US$232 billion in 2007 to US$966 billion in 2021 for adults aged 20–79 years (1,2). In addition to the direct health care costs, the indirect costs due to lost productivity are also considerable and may contribute an additional 30%–50% in estimating total costs (3,4). These health and economic challenges highlight the need for high-value, preventive health care interventions (5).

Approaches to weight management are undergoing a dramatic shift with the arrival of novel antiobesity medications, including the second-generation glucagon-like peptide 1 receptor agonist (GLP-1RA) semaglutide and dual GLP-1RA/glucose-dependent insulinotropic polypeptide receptor agonist tirzepatide. Superior efficacy of semaglutide, a novel GLP-1RA, has been demonstrated in reducing HbA_{1c} levels and body weight in comparison with alternative treatments like liraglutide and sitagliptin, while also reducing cardiovascular risk, in individuals with T2D (6–9). Despite these clinical benefits, its economic value remains uncertain. Although a previous review explored the cost-effectiveness of semaglutide in T2D management (10), numerous economic evaluations have been published since 2021, necessitating an updated analysis. Additionally, there is limited evidence on the potential relationships between findings on cost-effectiveness and study location, study sponsorship, discounting, time horizon, perspective, and type of comparator. This gap highlights the need for a comprehensive and systematic evaluation of semaglutide's economic value in T2D management.

This study addresses current evidence gaps in providing a comprehensive systematic review of the cost-effectiveness of semaglutide for T2D management. Specifically, this article addresses the following research questions:

- What is the economic value of semaglutide in comparison with other drugs for T2D management?
- How does the cost-effectiveness of semaglutide vary across subgroups of region, sponsor type, perspective, time horizon, discount rate, and type of comparators?

In addressing these questions, this work may provide valuable insights into the economic implications of using semaglutide for T2D management. These findings may inform future health economic evaluations and subsequent decision-making in diverse health care settings (11).

RESEARCH DESIGN AND METHODS

Study Protocol

The research protocol was registered on International prospective register of systematic reviews (PROSPERO) (identifier CRD42024504714 [available at https://www.crd.york.ac.uk/PROSPERO/view/CRD42024504714]). Initially, we intended to comprehensively and systematically review all economic evidence (including partial and full economic evaluations) related to the use of semaglutide in T2D management; however, during the full-text screening stage, significant heterogeneity in cost data across different health care settings prompted us to narrow the scope. Consequently, this article focuses exclusively on full economic evaluations, specifically, cost-effectiveness and cost-utility analyses (CUAs). The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (12).

Data Sources and Searches

The literature search covered two key biomedical databases, PubMed and Embase, and one economic database, the Cost-Effectiveness Analysis Registry (CEA Registry). Furthermore, to ensure comprehensive coverage of the relevant literature, we manually conducted a backward search by checking references and a forward search by examining citations. The initial search was conducted on 8 September 2023 and was updated on 11 June 2024 to include the most recent developments.

The search strategies, developed in consultation with a research librarian at Queensland University of Technology, were further refined in identifying relevant free-text terms from the recent analogous systematic review (10). The search terms consisted of "cost effectiveness," "semaglutide," and their synonyms. A full list of search terms can be found in Supplementary Table 1.

Eligibility Criteria

Studies were included if they met the following criteria.

1. Participants: studies involving populations living with T2D regardless of obesity status.
2. Intervention: semaglutide in any dosage (e.g., 1, 2, and 14 mg) or route of administration (e.g., oral daily and injection once weekly).
3. Comparator: studies with comparisons between semaglutide and other medications.
4. Outcomes: studies reported incremental cost-effectiveness ratio (ICER) or incremental cost-utility ratio (ICUR) outcomes of semaglutide versus other medications as the primary outcomes or secondary outcomes.
5. Study design: CUA (with cost per quality-adjusted life-year [QALY] gained as study outcome) or cost-effectiveness analysis (CEA) (with cost per effectiveness [e.g., percent reduction in HbA_{1c} or cardiovascular events] as study outcome) with trial-based or model-based methodologies.

Specifically, the following were excluded:

- Studies that did not include sufficient cost-effectiveness data for ICER or ICUR outcomes.
- Studies where semaglutide was compared with interventions other than other antiobesity drugs, such as bariatric surgery and lifestyle management.
- Studies limited to cost-of-illness studies, cost consequence analysis, cost-minimization analyses, budget impact analyses, or other partial economic evaluations that only considered costs or effectiveness without integrating both.
- Cost-of-control studies and cost-benefit analyses.

- Reviews, commentaries, letters, conference abstracts, editorials, and case reports.

Study Selection

A two-step screening process was performed to retrieve eligible studies. First, two coauthors (Z.L. and Q.X.) independently screened the titles and abstracts to identify potential articles according to inclusion criteria, aiming to keep as many relevant articles as possible. Next, the same two coauthors independently assessed the full text of the remaining studies to determine their eligibility based on the inclusion criteria. Discussion was conducted wherever necessary to reach a final decision in case of any discrepancies. Data screening was conducted on the Rayyan platform (https://www.rayyan.ai/), and all of the included references were managed in EndNote 21.

Data Extraction and Quality Assessment

Data Extraction

Two coauthors (Z.L. and B.Z.) independently extracted data using a predefined extraction form in Microsoft Excel software. Any discrepancies were resolved through discussions between the two coauthors, and if consensus could not be reached, the third coauthor (Q.X.) was consulted to reach resolution. The key elements are as follows:

- Study characteristics: first author, publication year, publication journal, country, continent (Europe, North America, Asia), and sponsorship (no sponsorship, sponsored by nonprofit organization/foundation/university, sponsored by Novo Nordisk, sponsored by other pharmaceutical industries).
- Model characteristics: currency year and country, discount rate used, perspective (health care payer/sector, broader [limited societal/societal] perspective), time horizon, willingness-to-pay (WTP) threshold, intervention, comparator, and targeted population.
- Model inputs: model cohorts starting age, proportion female sex, baseline BMI, and baseline HbA_{1c} value; the route of administration (mode oral, injection; frequency once weekly, once daily), health state utilities (HSUs); and relevant costs.
- Model results: base case results including costs, QALYs, and ICERs, along with factors influencing model results based on deterministic sensitivity analysis (DSA) and robustness based on probabilistic sensitivity analysis.
- Model limitations as reported.

Assessment of Reporting Quality. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist was used to assess the reporting quality of included studies (13). CHEERS 2022 is a standardized tool consisting of 28 key reporting items across several domains, including study title, abstract, background, methods, results, and discussion. Studies are evaluated based on these equally weighted items, with quality categorized as high ($\geq$75.0%), moderate (50.0%–74.0%), or low ($\leq$50.0%) (14). The scoring is based on fulfillment compliance: 1 point for full compliance (yes), 0.5 points for partial compliance (somewhat), and 0 points for noncompliance (no). Attributes deemed not applicable are excluded from the total. Two coauthors (Z.L. and B.Z.) independently performed the quality assessment, with any discrepancies resolved through discussions with a third coauthor (Q.X.).

Data Synthesis and Analysis

A descriptive summary of the study characteristics was first created to present an overview of the included studies, including year of publication, country, model type and parameters, sponsorship type, and study's reporting quality. Next, lifetime costs (converted into 2024 U.S. dollars) and lifetime QALYs were evaluated and synthesized. For presentation of the base case results (without cost conversion in ICERs) from the literature, the proportions of ICER outcomes (categorized as dominant, cost-effective, and not cost-effective) were calculated based on the WTP threshold reported in each included study. Furthermore, subgroup analyses were conducted based on region, study sponsor type, perspective, time horizon, discount rate, and comparator type. In addition, we conducted a sensitivity analysis (with cost conversion in ICERs) by applying a WTP threshold of US$50,000 (2024). Finally, the key factors influencing model results based on DSA were summarized, and model limitations were discussed.

Data and Resource Availability

All data are reported in the manuscript or the Supplementary Material.

RESULTS

Eligible Studies

A total of 1,360 records were initially retrieved from three databases: 300 from PubMed, 1,002 from Embase, and 58 from the CEA Registry. After removal of 313 duplicate records, 1,047 articles remained for title/abstract screening. Subsequently, 90 articles were assessed for eligibility, with 47 excluded for reasons such the following: conference abstracts (n = 10), cost-of-control analyses (n = 11), studies not for semaglutide or T2D patients (n = 25), or non–English language (n = 1). Additionally, 2 articles identified through backward searching were included, resulting in a final total of 45 full-text articles (2 CEAs and 43 CUAs) covering 119 comparisons (114, cost per QALY, and 5, cost per HbA_{1c} reduction). The full list of included studies is provided in Supplementary Table 2, and a detailed depiction of the selection process can be found in Fig. 1.

Characteristics of Included Studies

Table 1 provides a summary of the characteristics of the 45 included studies, ranging from 2019 to 2024. Detailed characteristics for each study are reported in Supplementary Table 3.

Of 45 articles, more than half (n = 24 [53.3%]) were conducted in Europe, 28.9% (n = 13) in North America (U.S. and Canada), and 17.8% (n = 8) in Asia (only in China). The target population mainly involved T2D patients with inadequate glycemic control, particularly those with T2D managed with metformin (n = 16) or other glucose-lowering medications (n = 10). Of the articles specifying the mode of administration, 14 included evaluation of the cost-effectiveness of injectable semaglutide, while 20 focused on its oral form.

Regarding the model perspective, 38 studies included adoption of a health care payer or sector perspective, 3 evaluation of both limited societal and health care payer views, and the rest a limited societal perspective. Of these 45 articles, a significant majority (93.3%) included adoption of a lifetime horizon and only 3 shorter-term horizons: 1 a 3-year horizon (15) and 2 a 52-week horizon (16,17). The most common discount rate was 3.0% (n = 13 [28.9%]), closely followed by 5.0% (22.2%) and 3.5% (22.2%). Two Canadian studies stand out with a 1.5% discount rate (18,19), and in two studies from the Netherlands discount rates of 1.5% and

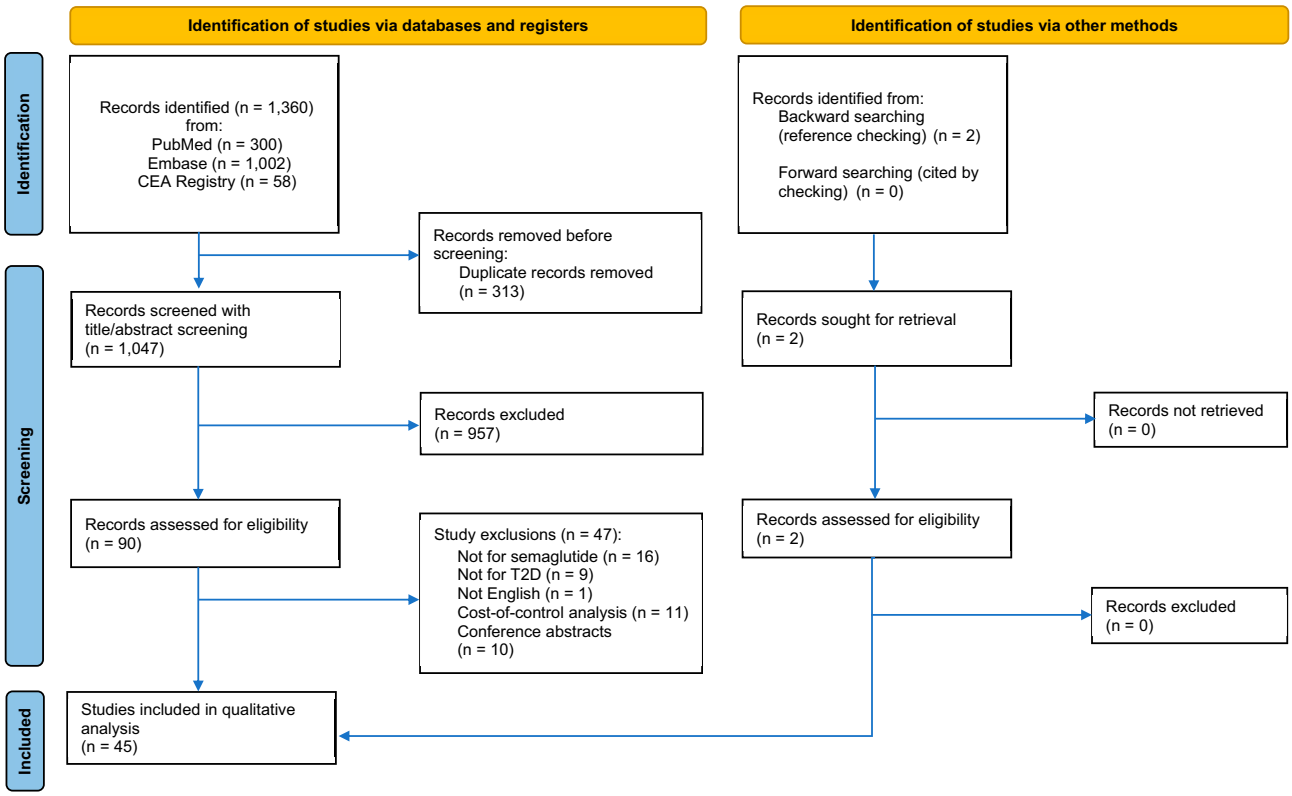

Figure 1—Flowchart of the study selection.

4.0% were applied for outcomes and costs, respectively (20,21). Discounting was not applied in two studies with a short-term time horizon of 52 weeks (16,17).

More than half of studies (*n* = 31 [68.9%]) were supported by medical device or pharmaceutical industry, and Novo Nordisk is the most common sponsor (*n* = 26). Other sponsors, including Boehringer Ingelheim and Eli Lilly, have funded five studies. Additionally, 11 studies were sponsored by nonprofit organizations and 1 study received no funding.

For the demonstrated reporting quality as assessed with the CHEERS 2022 checklist, the majority of the studies were of high quality. Specifically, 40 studies (88.9%) were classified as high quality, 3 as moderate quality, and only 2 as low quality (Table 1). Detailed assessment is provided in the attached CHEERS 2022 checklist.

Model Parameters

Model inputs and data sources are reported in Supplementary Table 4. Most model cohorts were derived from clinical trials such as the Peptide Innovation for Oral New Early Efficacy and Reducing Study (PIONEER), Study of Tirzepatide in the Management of Type 2 Diabetes (SURPASS), and Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) trials (*n* = 36), while in five studies data of clinical trials and network meta-analysis were integrated. The UK Prospective Diabetes Study (UKPDS) outcome model (*n* = 40) was the primary source for health outcomes/events, especially the UKPDS 68 equation (*n* = 17) and the UKPDS 82 equation (*n* = 8). In ∼86.7% of studies HSUs were obtained through literature reviews, with the EuroQol-5 Dimensions (EQ-5D) being the most frequently used instrument (*n* = 37), followed by Time Trade-Off (TTO) (*n* = 4) and Health Utilities Index Mark (HUI) (*n* = 3).

The average starting age of the model cohorts was generally between 55 and 65 years. Sex distributions were balanced, ranging from 39.5% to 56.8% female. Baseline BMI ranged from 26.5 to 41.0 kg/m^2, and baseline HbA_{1c} levels ranged from 8.0% to 8.8%. The most commonly used baseline HSU was 0.79, with variation for HSUs from 0.71 to 0.94.

Lifetime Costs and QALYs

The lifetime costs, converted into 2024 US$for comparability, are presented in Supplementary Table 5. On average, the lifetime cost for semaglutide was US$114,431, ranging from US$25,205 to US$434,749. Subgroup analysis by region indicated that the lifetime cost for semaglutide in North America is significantly higher, approximately twice that in Europe and four times that in China. For studies with different sponsors, semaglutide in North America was found to be cheaper in studies that were funded by Novo Nordisk in comparison with the findings of those with no sponsor or those funded by other industry sponsor.

Table 2 shows the average lifetime QALYs for semaglutide and QALY differences (semaglutide vs. other medications), overall and with subgroups by region, study sponsor type, perspective, discount rate, and type of comparator. The number of overall lifetime QALYs was 9.69 (range 4.03–14.98), with a QALY difference of 0.17 (–0.15 to 1.02). There was notable regional variation in QALY difference: highest for North America (0.29), moderate for Europe (0.15), and lowest for China (0.06). Subgroup analysis by sponsorship indicated that the QALY differences in studies that were sponsored by other companies were negative, specifically for those in North America.

Base Case ICERs

Figure 2 demonstrates the distribution of model base case results for semaglutide in comparison with other medications,

Table 1—Basic characteristics (*N* = 45)

	No. of studies	Percentage
Study type		
CEA (cost per HbA_{1c} reduction)	2	4.4
CUA (cost per QALY)	43	95.6
Year		
2019	9	20.0
2020	6	13.3
2021	8	17.8
2022	9	20.0
2023	11	24.4
2024	2	4.4
Country		
U.S. (North America)	10	22.2
U.K. (Europe)	9	20.0
China (Asia)	8	17.8
Denmark (Europe)	4	8.9
Canada (North America)	3	6.7
Spain (Europe)	3	6.7
Sweden (Europe)	2	4.4
Netherlands (Europe)	2	4.4
Portugal (Europe)	2	4.4
Estonia (Europe)	1	2.2
Slovakia (Europe)	1	2.2
Perspective		
Health care payer/sector	38	84.4
Limited societal	4	8.9
Both	3	6.7
Time horizon		
52 weeks	2	4.4
3 years	1	2.2
Lifetime	42	93.3
Discount rate		
1.5%	2	4.4
3.0%	13	28.9
3.5%	10	22.2
4.0%	4	8.9
5.0%	10	22.2
1.5% (outcome) and 4% (costs)	2	4.4
Not applicable#	2	4.4
Not reported*	2	4.4
Sponsor type		
Nonindustry sponsorship	11	24.4
Sponsored by Novo Nordisk	26	57.8
Sponsored by other drug companies$	5	11.1
No sponsor	1	2.2
Not reported	2	4.4
Type of comparator&		
GLP-1RA	29	64.4
SGLT2i	20	44.4
DPP-4i	9	20.0
Others	8	17.8
Reporting quality (CHEERS 2022 checklist)		
Low (≤50%)	2	4.4
Moderate (50%–74%)	3	6.7
Good (≥75%)	40	88.9

#Not applicable indicates that no discounting was conducted due to the short-term time horizon (52 weeks) used in these two studies. *These two cost-utility analyses with a lifetime horizon reported discounted outcomes but failed to report the discount rates. Therefore, the discount rate in the official guideline (U.K. 3.5% and U.S. 3.0%) were used for the subgroup analyses by discount rate in Fig. 2 and Supplementary Tables 7 and 8. $Other drug companies mainly includes Boehringer Ingelheim and Eli Lilly. &The total exceeds 45 as the categories are not mutually exclusive.

overall and for subgroups of region, study sponsor type, perspective, time horizon, discount rate, and type of comparator.

Among the findings of 119 comparisons, semaglutide was dominant in 26.9% (*n* = 32), cost-effective in 47.1% (*n* = 56), and not cost-effective in 26.1% (*n* = 31). Probabilistic sensitivity analysis results suggested that, for studies proving cost-effective, probability of semaglutide being cost-effective ranged from 50.0% to 100.0%. In contrast, for those suggesting that semaglutide was not cost-effective, probability varied from 0.0% to 50.0% (Supplementary Table 6).

Region

Strong evidence indicated more value for money for semaglutide in Europe, with only 7.0% of studies indicating that semaglutide is non–cost-effective. However, semaglutide was more likely to be deemed non–cost-effective in China (Fig. 2 and Supplementary Table 7).

Sponsorship

In studies sponsored by Novo Nordisk, semaglutide had clear advantages over other medications (dominance or cost-effectiveness in all 66 comparisons). Conversely, in studies sponsored by other pharmaceutical companies (*n* = 9, all from Europe and North America), semaglutide was less favorable. For studies funded by nonprofit organizations (*n* = 44), semaglutide was dominant or cost-effective in 50.0% of cases, ranging from 29.4% in China to 63.0% in North America (Fig. 2).

Perspective

Figure 2 shows that, for studies with adoption of a health care payer/sector perspective, semaglutide was dominant in 25.0%, cost-effective in 44.0%, and not cost-effective in 31.0%. When a broader (limited societal or societal) perspective was used, semaglutide was either cost-effective (63.2%) or dominant (36.8%) over other medications (Supplementary Table 7).

Time Horizon

In studies with a shorter time horizon, semaglutide was dominant in 16.7% and not cost-effective in 33.3%; however, for those adopting a lifetime horizon, the figures were 27.4% and 25.7%, respectively. Notably, subgroup analysis (of studies adopting a lifetime horizon) showed that semaglutide was less likely to be cost-effective or dominant in China (42.9%) than Europe (93.0%) or North America (62.9%).

Discount Rate

For findings of studies where a discount rate was applied (for all studies a lifetime

Table 2—Lifetime QALYs (for semaglutide) and QALY differences (semaglutide versus other drugs)*

	No. of studies	No. of comparisons	Average QALY (min, max)	QALY difference (min, max)
Overall	42	113	9.69 (4.03, 14.98)	0.17 (−0.15, 1.02)
By region				
Europe	24	57	9.17 (6.58, 12.12)	0.15 (−0.02, 0.43)
North America	10	35	10.05 (4.03, 14.98)	0.29 (−0.13, 1.02)
China	8	21	10.47 (7.31, 12.56)	0.06 (−0.15, 0.26)
By sponsorship				
Nonindustry				
Overall	11	38	9.77 (4.03, 13.13)	0.26 (−0.15, 1.02)
Europe	0	0	NA	NA
North America	5	21	8.41 (4.03, 13.13)	0.47 (0.06, 1.02)
China	6	17	11.14 (9.63, 12.56)	0.04 (−0.15, 0.26)
Novo Nordisk				
Overall	26	66	9.64 (6.58, 14.98)	0.16 (−0.01, 0.43)
Europe	21	53	9.17 (6.58, 12.12)	0.16 (0.03, 0.43)
North America	3	9	13.09 (11.10, 14.98)	0.17 (−0.01, 0.37)
China	2	4	7.62 (7.31, 7.91)	0.16 (0.08, 0.22)
Other drug companies				
Overall	5	9	9.71 (8.78, 10.24)	−0.04 (−0.13, 0.13)
Europe	3	4	9.11 (8.78, 9.25)	0.04 (−0.02, 0.13)
North America	2	5	10.19 (10.15, 10.24)	−0.10 (−0.13, –0.06)
China	0	0	NA	NA
By perspective				
Narrow (health care payer/sector)				
Overall	38	94	9.50 (4.03, 14.98)	0.17 (−0.15, 1.02)
Europe	21	42	8.87 (6.58, 10.41)	0.13 (−0.02, 0.43)
North America	9	31	9.67 (4.03, 14.98)	0.31 (−0.13, 1.02)
China	8	21	10.47 (7.31, 12.56)	0.06 (−0.15, 0.26)
Broader (limited societal/societal)				
Overall	7	19	10.68 (8.00, 14.98)	0.20 (0.03, 0.43)
Europe	5	15	10.08 (8.00, 12.12)	0.20 (0.07, 0.43)
North America	2	4	12.64 (11.10, 14.98)	0.20 (0.03, 0.37)
China	0	0	NA	NA
By discount rate				
Not >3.5%				
Overall		84	9.66 (4.03, 14.98)	0.21 (−0.13, 1.02)
Europe	18	49	9.39 (6.58, 12.12)	0.16 (−0.02, 0.43)
North America	11	36	10.05 (4.03, 14.98)	0.29 (−0.13, 1.02)
China	0	0	NA	NA
>3.5%				
Overall	14	29	9.76 (7.18, 12.56)	0.07 (−0.15, 0.26)
Europe	6	8	7.91 (7.18, 9.16)	0.09 (0.03, 0.20)
North America	0	0	NA	NA
China	8	21	10.47 (7.31, 12.56)	0.06 (−0.15, 0.26)
By type of comparator				
GLP-1RA				
Overall	27	52	9.86 (4.03, 12.98)	0.05 (−0.15, 0.31)
Europe	14	21	9.10 (6.59, 11.63)	0.08 (0.03, 0.30)
North America	6	12	10.02 (4.03, 12.98)	0.02 (−0.13, 0.31)
China	7	19	10.44 (7.31, 12.56)	0.05 (−0.15, 0.24)
SGLT2i				
Overall	18	30	9.51 (4.03, 14.98)	0.16 (−0.02, 0.37)
Europe	13	21	9.06 (7.18, 10.63)	0.14 (−0.02, 0.23)
North America	4	8	10.81 (4.03, 14.98)	0.26 (0.06, 0.37)
China	1	1	11.11	0.10
DPP-4i				
Overall	8	14	8.30 (4.03, 10.41)	0.26 (0.11, 0.43)
Europe	6	12	9.00 (8.00, 10.41)	0.26 (0.11, 0.43)
North America	2	2	4.07 (4.03, 4.11)	0.31 (0.3, 0.31)
China	0	0	NA	NA

*For 43 CUA studies using cost per QALY as the study outcome, only one study was not based on a lifetime horizon, so lifetime QALYs was summarized in this table. NA, not applicable.

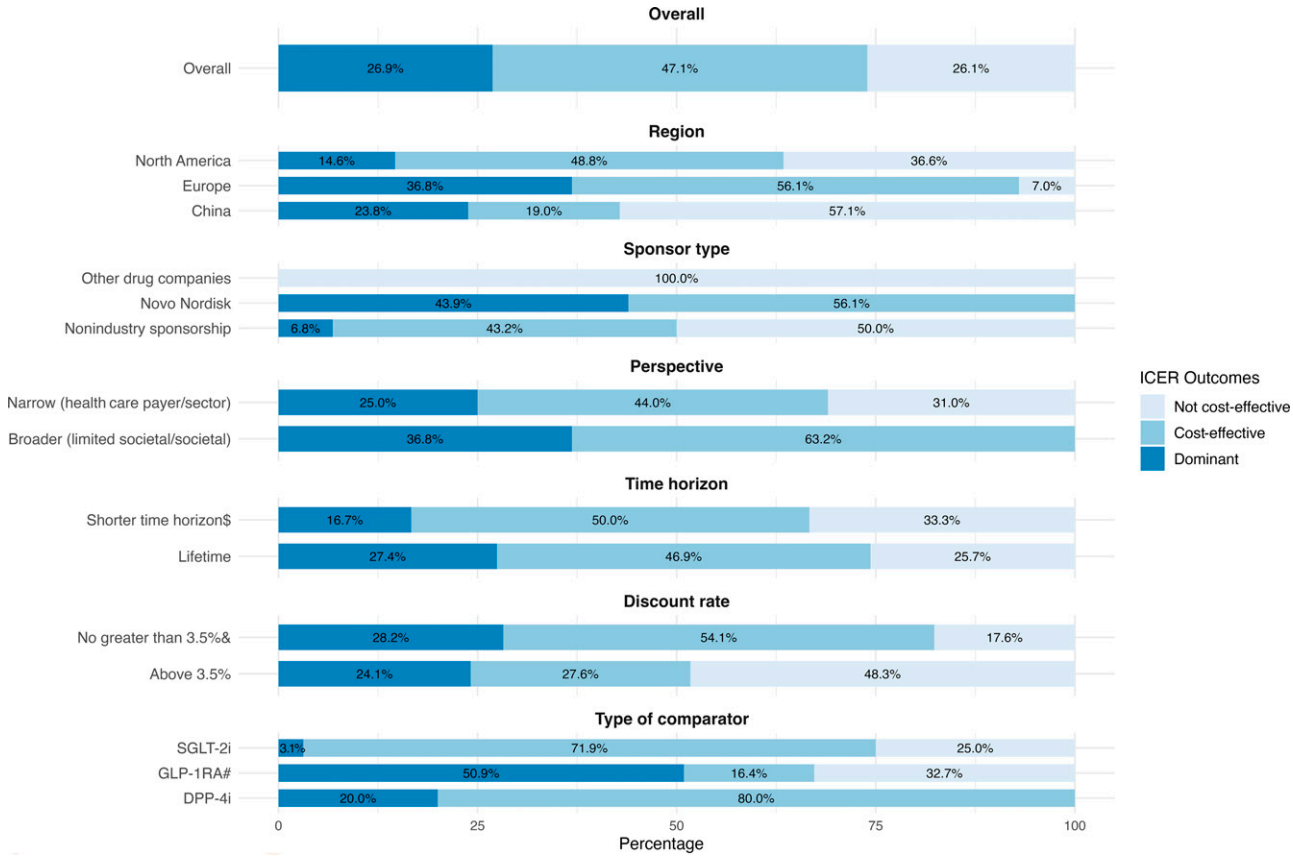

Figure 2—Base case ICERs. The base case results were determined based on the reported willingness to pay threshold in each study. The category Dominated was merged into Not cost-effective. #Semaglutide was dominated by tirzepatide in all 10 comparisons (7 from the U.S. and 3 from China) involving the two drugs within the subcategory GLP-1RA. $The category Shorter time horizon included two CEA studies adopting a time horizon of 52 weeks (used cost per 1% reduction in HbA_{1c} or cost per 1 kg weight loss as study outcome) and one CUA study of 3 years' time horizon, all from the U.S. &Two cost-utility analyses with a lifetime horizon reported discounted outcomes but failed to report the discount rates. Therefore, the discount rates in the official guideline (U.K. 3.5% and U.S. 3.0%) were used for the subgroup analyses. Details are reported in Supplementary Tables 7 and 8. ICEA, incremental cost effectiveness ratio.

horizon was adopted, except one with a 3-year horizon), semaglutide was less likely to be cost-effective in those with a higher discount rate (all from Europe [42.9%] and China [57.1%]) than in those with a lower discount rate (all from Europe [62.1%] and North America [37.9%]).

Type of Comparator

Compared with other GLP-1RAs (n = 55), semaglutide was dominant in 50.9% of studies, cost-effective in 16.3%, and not cost-effective in 32.7%. However, the advantage is notably higher in Europe (100.0%) in comparison with North America (53.3%) and China (42.1%). Notably, semaglutide was dominated by tirzepatide in all 10 comparisons (10 of 55) involving the two drugs. In comparisons against sodium–glucose cotransporter 2 inhibitors (SGLT2i) (n = 32), the corresponding figures were 3.1%, 71.9%, and 25.0%. In comparisons with dipeptidyl peptidase 4 inhibitors (DPP-4i) (n = 15), semaglutide was dominant in 20.0% and cost-effective in 80.0% of all cases.

Sensitivity Analysis

In applying a WTP threshold of US$50,000 per QALY, similar trends were observed for both overall and subgroup analyses (Supplementary Table 8). These results suggest that the base case findings are robust across varying thresholds and highlight the consistency of semaglutide's cost-effectiveness profile under different analytical assumptions.

Key Factors to Model Results Based on DSA

As shown in Supplementary Table 9, DSA was reported in 32 articles to investigate the key factors that sensitive to the model results. The results showed that HbA_{1c} reduction (n = 12), discount rate (n = 9), time horizon (n = 9), cost of semaglutide (n = 8), HbA_{1c} threshold (n = 7), and BMI reduction (n = 5) were the most important factors sensitive to model results.

Reported Model Limitations

Supplementary Table 10 summarizes the model limitations identified in each model. The most frequently reported model limitation was the uncertainty of model inputs, especially when long-term clinical outcomes were extrapolated from short-term data (n = 27). This issue raises concerns about the reliability of cost-effectiveness projections over extended horizons. Additionally, nine studies highlighted specific issues associated with the UKPDS model, including *1*) reliance on potentially outdated data (>20 years old), *2*) population characteristics that may not be reflective of current demographics, and *3*) that the model cannot be used for certain complications. Furthermore, in six articles a

limitation identified was use of network meta-analysis instead of clinical trial data for comparisons.

These limitations underscore the need for future studies to address these challenges through incorporation of updated input data and more representative population cohorts and prioritization of clinical trial evidence where feasible to enhance the validity of cost-effectiveness evaluations.

CONCLUSIONS

This article provides a comprehensive synthesis of the findings on cost-effectiveness of semaglutide in the treatment of T2D in comparison with other glucose-lowering medications, incorporating evidence up to 2024. Notably, for most included studies there was a lifetime horizon and high reporting quality was demonstrated. Semaglutide is generally demonstrated to be cost-effective in evaluations against within-study WTP thresholds, particularly in high-income countries, in studies funded by Novo Nordisk, and in those with adoption of a broader perspective, lower discount rate, and longer time horizon. Cost-effectiveness outcomes remained consistent with conversions with a common currency unit and WTP threshold $US 50,000. However, findings were sensitive to HbA_{1c} reduction, model time horizon, discount rates, and cost of semaglutide.

Regional Differences

The regional distribution of the studies reveals that current research is concentrated in North America (Canada and U.S.), Europe, and China, while other regions with a significant T2D burden remain underrepresented. For example, cost-effectiveness of semaglutide in Australia, which ranks fourth globally in T2D burden over the past 30 years, has not been studied (22). This lack of research limits the generalizability of findings and highlights the urgent need for studies in diverse health care settings to guide local resource allocation and management policies (23).

The heterogeneity in cost-effectiveness outcomes across regions may reflect differences in population characteristics, health care systems, and cost structures. However, the lack of detailed demographic data in the included studies limited our ability to conduct a more granular analysis directly based on population characteristics. Future researchers should aim to fill this gap by examining the economic implications of semaglutide in underrepresented regions and exploring how population-specific factors, such as ethnicity, health care access, and treatment practices, influence cost-effectiveness outcomes. Such efforts would provide a more comprehensive understanding of semaglutide's value and support more equitable resource allocation in diverse health care settings.

Impact of Sponsorship

Our analysis of studies with different funding sources highlights the potential influence of pharmaceutical sponsorship on assessment results. For all studies funded by Novo Nordisk, the developer of semaglutide, the reports were consistently of cost-effectiveness and dominance of semaglutide over other medications, often demonstrating more QALYs and QALY differences. Conversely, studies supported by other companies, such as Boehringer Ingelheim and Eli Lilly, presented opposing conclusions. These findings suggest that industry funding can lead to biased conclusions that favor the sponsor's drug, potentially influencing health care decisions and policies (24). In contrast, studies without industry sponsorship appeared to provide more objective results, with $>$60.0% indicating either dominance or cost-effectiveness of semaglutide.

Neglect of Broader Perspective

The perspective adopted in cost-effectiveness evaluations also plays a critical role in shaping outcomes. We found that analyses adopting a limited societal perspective showed a 100.0% support rate for semaglutide, significantly higher than that of evaluations from other perspectives, regardless of the country. This reveals that the broader societal benefits of semaglutide, particularly in managing T2D, become more apparent when productivity losses and societal impacts are considered. Since T2D affects society through both health care costs and lost productivity (25,26), a societal perspective can provide a more comprehensive understanding of the true value of treatments (27). However, many health economic analyses do not fully explore the societal perspective, which could encompass resources related to sectors such as the environment, education, or justice (28). Inclusion of all relevant groups and interests in evaluations could function to offer more insightful guidance for decision-makers (29).

The Role of Time Horizon and Discounting

Time horizon and discount rate are two additional critical model factors influencing the pharmacoeconomic assessment of semaglutide. Our study suggests that adopting a longer time horizon (e.g., lifetime) resulted in more favorable cost-effectiveness outcomes for semaglutide in comparison with short-term analyses. This is consistent with previous research, indicating that longer horizons can better capture the full spectrum of costs and benefits, including the reduction in complications and improvements in quality of life (30,31). However, real-world evidence suggests that treatment adherence and persistence with semaglutide are substantial factors, and decline over time (32,33). Economic evaluations where persistent long-term benefits are assumed, without these real-world adherence patterns accounted for, may overestimate semaglutide's cost-effectiveness. Future models should incorporate real-world discontinuation rates for improvement of the accuracy of long-term projections.

The use of discount rates in included studies aligned well with the local official guidelines; however, we found that lower discount rates generally produced more favorable results for semaglutide. This aligns with findings that reducing the positive discount rate to zero increases the relative cost-effectiveness of treatments (34). However, the optimal discount rate remains debated. Some experts recommend a $\leq$3.0% discount rate for both costs and outcomes for the health care sector and societal perspectives (35). Therefore, investigators are recommended to strictly follow the guidelines in the field in selecting discount rates and interpreting results to ensure the reliability of their economic evaluations.

Identified Factors Sensitive to Cost-effectiveness Outcome

In addition to time horizon and discount rate, the DSA identified cost of semaglutide, HbA_{1c} reduction, and BMI difference as crucial factors influencing the model results. HbA_{1c} reduction plays a vital role in reducing T2D-related complications, such as cardiovascular events and nephropathy, which decreases long-term health care costs (36,37). Enhancing HbA_{1c} control, whether

through dosage optimization or patient adherence strategies, could further increase the drug's economic value (38,39). Lowering the cost of semaglutide, through pricing negotiations or subsidies, significantly improve its cost-effectiveness profile, making it more accessible for health care systems (40). Similarly, BMI reduction contributes to the cost-effectiveness of semaglutide, as weight loss can mitigate obesity-related complications and enhance quality of life. Incorporating lifestyle interventions alongside semaglutide could amplify its benefits, resulting in more favorable health and economic outcomes.

Strengths and Limitations

This study has several limitations. First, only articles in English were considered in the review, which may have led to the exclusion of relevant articles in other languages. Second, as a retrospective systematic review, this study reflects only past and present research findings. For future trends, it cannot provide an accurate projection. Third, the critical drivers of CEA/CUA models, specifically, the effect estimates used (e.g., per-protocol or intention-to-treat effect) and the detailed cost components considered, are essential for interpreting and comparing model results. However, these details were often not explicitly reported in the studies reviewed, which limited the depth of analysis possible in this review. We recommend that in future studies investigators prioritize transparent reporting of these factors to improve the interpretability and robustness of economic evaluations. Additionally, while we conducted subgroup analyses exploring variations across regions, study sponsor types, and other factors, the lack of detailed demographic and health care system information in the included studies limited our ability to perform more granular analyses based on population-specific characteristics. Last, as mentioned above, most studies were conducted with adoption of a narrow health care perspective.

Despite these limitations, this work has notable strengths that make it a valuable contribution to the literature. This article offers a comprehensive and up-to-date synthesis of study findings on the cost-effectiveness of semaglutide for T2D management, incorporating evidence up to 2024. Unlike the previous review (10), this work includes a wide range of subgroup analyses, with examination of critical factors such as study sponsorship, perspective, time horizon, discounting, and comparator type, thereby providing a more nuanced and context-sensitive evaluation. Additionally, in applying a detailed quality appraisal with the CHEERS 2022 checklist, the review ensures a rigorous examination of reporting standards in the included studies. The high proportion of studies with demonstrated strong methodological and reporting quality reinforces the robustness of the conclusions. Sensitivity analyses further validated the reliability of the findings, showing consistent trends with different WTP thresholds and subgroup conditions. These efforts lend confidence to the economic evaluations and are supportive of the generalizability of the key insights to diverse health care contexts. This thorough approach not only informs health care decision-making and resource allocation for T2D management but also lays the groundwork for future research to refine economic evaluations and address existing gaps in the literature.

Summary of Recommendations

- There is a need for studies in regions outside Europe, North America, and China, for a more comprehensive understanding of the cost-effectiveness of semaglutide in different local health care contexts.
- In future research investigators should prioritize independent studies without industry sponsorship and ensure transparent reporting to validate the true economic value of semaglutide.
- In economic evaluations of semaglutide in T2D management a societal perspective should be adopted to capture semaglutide's broader benefits, including its impact on productivity and quality of life.
- A longer time (e.g., lifetime) horizon is recommended to more accurately reflect the long-term benefits and cost-effectiveness of semaglutide in managing T2D.
- Given the changes in semaglutide's pricing and the evolving risk of complications, dynamic economic models are needed to incorporate new data and provide a more accurate assessment of its long-term economic value.

Conclusion

This review demonstrates that in evaluations against the WTP thresholds used in the individual studies, semaglutide is generally cost-effective compared with other glucose-lowering medications. However, cost-effectiveness outcomes varied by study sponsorship type, perspective, discount rate, time horizon, and comparator type. The findings highlight the need for region-specific, context-sensitive analyses, along with transparent and unbiased reporting, to inform evidence-based health care decision-making.

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