Received: 28 January 2025 | Revised: 5 March 2025 | Accepted: 13 March 2025

DOI: 10.1111/dom.16364

SPECIAL ISSUE ARTICLE

WILEY

Real-world evidence on the utilization, clinical and comparative effectiveness, and adverse effects of newer GLP-1RA-based weight-loss therapies

Reimar W. Thomsen PhD[1] | Aurélie Mailhac MSc[1] | Julie B. Løhde MD[2,3] | Anton Pottegård DMSc[4]

[1]Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

[2]Department of Biomedicine, Aarhus University, Aarhus, Denmark

[3]Steno Diabetes Center Aarhus, Aarhus, Denmark

[4]Department of Public Health, Clinical Pharmacology, Pharmacy, and Environmental Medicine, University of Southern Denmark, Odense, Denmark

Correspondence
Reimar W. Thomsen, Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus, Denmark.
Email: rwt@clin.au.dk

Anton Pottegård, Department of Public Health, Clinical Pharmacology, Pharmacy, and Environmental Medicine, University of Southern Denmark, Odense, Denmark.
Email: apottegaard@health.sdu.dk

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as key agents for weight management, based on their marked efficacy as observed in randomized controlled trials. While still limited, real-world studies on GLP-1RA use in populations with obesity are increasingly available. This narrative review discusses contemporary real-world evidence demonstrating the utilization, clinical and comparative effectiveness, and adverse effects of the currently approved GLP-1RA-based weight-loss therapies, that is, liraglutide, semaglutide and tirzepatide. The observed weight reduction in clinical practice overall tends to be lower than in randomized controlled trials; however, outcomes approach those seen in trials when focusing on highly adherent patients. Real-world studies demonstrate high discontinuation rates of GLP-1RAs (20%–50%) within the first year, and the use of much lower doses than those evaluated in clinical trials. Evidence from observational studies within type 2 diabetes or obesity populations suggests frequent gastrointestinal disturbances in GLP-1RA users, as also observed in trials, but no clear increase in risks of severe events like pancreatitis or pancreatic cancer, thyroid disorders, or depression and self-harm. Further evidence is needed to understand possible real-world associations of GLP-1RAs with eye disease and other rare outcomes. We provide 10 areas of particular importance for further research on GLP-1RA within the real-world space, including improved understanding of the exact drivers of early discontinuation and suboptimal dosing, studies of the effects of stopping GLP-1RA treatment, and investigations of clinical and cost-effectiveness for hard clinical outcomes in real-world settings, including not only cardio-reno-metabolic outcomes but also obesity-induced diseases like neuropsychiatric disease, cancer, musculoskeletal disease, and infections.

Plain Language Summary

Recent advancements in weight-loss medications have sparked a lot of interest. The so-called GLP-1 receptor agonist medications (GLP-1RAs) have gained a lot of attention, because they have shown to be very effective, leading to significant weight loss

in patients participating in clinical trials. GLP-1RAs, like liraglutide, semaglutide, and tirzepatide, help manage weight by mimicking hormones that control blood sugar and appetite. However, how these medications perform in real life can be different from the controlled settings of clinical trials, in which patients are carefully selected and their treatment plans closely followed. This literature review looks at how these medications are used and their effectiveness and safety in real-world settings. In real-life practice, GLP-1RAs are often less effective than in clinical trial conditions. This is usually because patients don't follow their medication plans as strictly as in trials. Real-world data shows that many patients use lower doses and do not stick to their treatment as strictly as participants in a controlled trial might, leading to less weight loss. However, those who do follow their plans closely can achieve results similar to those in trials. A major issue with GLP-1RAs is that many patients stop using them within the first year due to side effects or high costs of the medications, especially if not covered by insurance. Common side effects include nausea and digestive problems, which are the main reasons patients stop taking these treatments. These side effects are often manageable and decrease over time, and this reviews found no strong real-world evidence that GLP-1RAs cause severe side effects in many users. Despite these challenges, when GLP-1RAs are used effectively and consistently, they show substantial benefits in weight loss, most so the newest medications semaglutide and tirzepatide. These medications are also likely to help manage and prevent weight-related health conditions like type 2 diabetes and cardiovascular disease, but evidence for these beneficial outcomes is still scarce in real-world settings. The review emphasizes the need for more research to understand why many patients stop using these medications and how to improve dosing. It also calls for studies on the long-term effects of these therapies on various health outcomes, including mental health, cardiometabolic health, cancer, and rare conditions like eye diseases. Overall, while GLP-1RAs are a valuable tool for weight management, their real-world use requires careful consideration of individual patient factors, such as the ability to stick to treatment plans, manage side effects, and afford the medications. Further research will help make these treatments more effective for a wider range of people that need them.

KEYWORDS

drug safety, drug utilization, epidemiology, glucagon-like peptide-1 receptor agonists, medications for obesity, real-world evidence, treatment adherence, treatment outcomes, weight loss

1 | INTRODUCTION

The global prevalence of obesity has reached alarming levels, with significant implications for public health.[1–3] According to the World Health Organization (WHO), more than 1 billion people worldwide are now affected by obesity, defined as a body mass index (BMI) ≥30.[4] Obesity is associated with numerous comorbidities, including metabolic syndrome, type 2 diabetes (T2D), cardiovascular disease, kidney disease, liver disease, sleep apnoea and other respiratory diseases, musculoskeletal diseases, mental illness and many types of cancer, which collectively contribute to increased morbidity and mortality and a huge economic burden associated with obesity.[5,6]

Traditional weight-loss strategies, such as lifestyle behavioural interventions, often yield only limited weight loss and struggle to maintain a clinically relevant weight loss over time.[7,8] Consequently, there is considerable interest in new approaches to achieve and maintain substantial weight loss, including emerging pharmacological options.[9,10] Among these, incretin hormone-based drugs, first and foremost glucagon-like peptide 1 receptor agonists (GLP-1RA),[11]

have emerged as a pivotal treatment option for managing both obesity and T2D.[12–15] A surge in the use of GLP-1RA has thus occurred in many countries over the last 3–4 years, even leading to periods of global supply shortage.[16] As of early 2025, GLP-1RA marketed for the management of obesity include liraglutide, semaglutide, and the newer dual GLP-1RA and glucose-dependent insulinotropic polypeptide receptor agonist (GIP-RA) tirzepatide,[8] while a range of new single, dual and triple hormone agonists are currently under development.[14]

The three GLP-1RA-based agents currently approved for weight loss have all shown clear efficacy in promoting weight loss in randomized controlled trials (RCTs),[17–19] that is, in settings with good medication adherence among participants and a follow-up of typically one to two years.[15] In contrast, evidence on their long-term effects and hard clinical outcomes in broad populations with obesity in real-world clinical practice is still limited, and comparably little is known about the utilization patterns and clinical effects on both weight loss and associated comorbidities of these newer medications in the population-based setting.[7,14,20,21]

The goal of this narrative review is to summarize available evidence from real-world observational studies on the utilization patterns, clinical and comparative effectiveness, and adverse effects of the three currently approved GLP-1RA for weight loss, that is, liraglutide, semaglutide and tirzepatide. The review briefly discusses contemporary real-world data on drug utilization and then focuses on evidence on clinical outcomes in routine care settings, including weight loss, other clinical outcomes and adverse effects. We focus mainly on larger observational epidemiological studies, with a prioritization of studies conducted in obese populations (if available), and secondarily in T2D populations, to ensure the relevance, robustness and timeliness of the data. Further, we highlight unmet research needs and potential future directions in the study of the real-world effects of these novel weight-loss medications.

2 | METHODS

2.1 | Search strategy

To identify relevant studies for this literature review, a search was conducted across PubMed and the Cochrane Library. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH) terms related to obesity, pharmacological weight-loss therapies, drug utilization and safety, clinical effects, and cost-effectiveness. Keywords included 'obesity/drug therapy', 'body weight', 'overweight', 'weight loss,' 'anti-obesity agents', 'incretins', 'glucagon-like peptide-1 receptor agonists', 'epidemiologic studies', 'systematic review', 'pharmacoepidemiology', 'health services research', 'drug utilization', 'treatment adherence and compliance', 'adverse effects', 'prognosis' and 'treatment outcome'. Boolean operators (AND, OR) were used to refine the search results. Searches were run in January 2025 and limited to studies published in English until 15 January 2025. A hand search of the bibliographies of eligible publications was also undertaken to identify any relevant studies that were not found by the original search.

Priority was given to evidence obtained from recent observational epidemiologic studies (case series, cohort, case–control and cross-sectional studies), preferably of more than a few hundred individuals. We prioritized studies of GLP-1RA-based drug use in populations with obesity, but we also assessed prior systematic literature reviews and recent large studies of GLP-1RA use in populations with T2D, as evidence for various outcomes is still scarce for populations with obesity. Where relevant, we compared the observational evidence with that of meta-analyses of GLP-1RA RCTs or major individual RCTs. Data extraction included study characteristics (e.g., author, year, country), study populations and data sources, study type and methodology, details of the pharmacological interventions, study duration, outcomes related to utilization (e.g., prescription trends, adherence), clinical effects (e.g., weight loss, metabolic control, clinical outcomes) and adverse events.

3 | UTILIZATION OF GLP-1RA

Population-based studies from the United States (US) and Europe have documented substantial increases in anti-obesity medication use during the last decade,[16,22–24] accelerating with the introduction of semaglutide and tirzepatide for weight loss.[16] In major weight loss RCTs, 65%–85% of participants adhered to the treatment with liraglutide, semaglutide, or tirzepatide, usually achieving target doses.[19,25,26] However, GLP-1RA treatments showed over twice the odds of discontinuation due to adverse events compared with placebo.[27] Participants in RCTs are carefully selected and monitored in highly controlled environments, with close counselling by caregivers and no financial limitations on drug therapy, helping optimal adherence. In everyday clinical care, users are more likely to skip doses, take less than the prescribed amount, or not fill their prescriptions at all, due to factors like suboptimal insurance coverage, financial constraints, periodically limited drug accessibility, side effects and physician–patient barriers.[28] As recently reviewed,[28] lower education, lower income, older age and non-White race are associated with 10%–50% lower odds of receiving GLP-1RA versus other diabetes therapies in real-world patients with T2DM. For T2D populations, studies suggested persistent drug use (i.e., no full discontinuation) in about 80% of users after 1 year in European settings,[29,30] but only in about 50% in Israel[31] and the United States.[32]

Among people with obesity, there is evidence that GLP-1RA discontinuation is even higher than in people with T2D.[33,34] A recent US study of 4066 obese people without T2D initiating any GLP-1RA found only 32% therapy persistence at one year,[35] while three other US studies suggested therapy persistence in 35%–50% at 1 year.[33,34,36] In a Danish population-based cohort study of 110 749 initiators of semaglutide for obesity, about 50% persisted for one year.[37] Notably, only 10% followed the recommended semaglutide dose increases every four weeks, and only 12% reached the recommended target dose of 2.4 mg by their 5th prescription, with one in three users continuing with the low 1.0 mg dose for a prolonged time.[37] Our own unpublished data

suggest that early discontinuation of semaglutide for weight loss is linked to low-income areas, mental health issues, other comorbidities and younger age.[38] Without insurance coverage, many initiators of semaglutide and tirzepatide cannot afford long-term treatment,[28] which is concerning given the higher obesity burden and treatment needs among those with lower socio-economic status, mental illness, obesity-related comorbidities and younger age.[39–41]

4 | EFFECTS OF GLP-1RA FOR WEIGHT LOSS

4.1 | Clinical guidelines for GLP-1RA therapies

Guidelines for the clinical management of people with obesity have generally lagged behind the rapid development of newer pharmacological therapies.[42,43] Existing guidelines have been reviewed recently by others, for example, Cornier,[9] Yurista[44] and Gaskin.[45] While newer cardiology guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) in 2019[46] and the European Society of Cardiology (ESC) in 2021[47] cover weight loss in cardiovascular disease prevention, and the 2020 Canadian clinical practice guideline on obesity in adults[48] offers good advice on assessment, prevention and treatment of obesity, these guidelines do not cover the most effective weight loss drugs currently in use, that is, semaglutide and tirzepatide.[27] The newer American Gastroenterological Association (AGA) guidelines[49] offer some guidance on the use of liraglutide and semaglutide.

4.2 | Clinical effectiveness of GLP-1RA for weight loss in real-world populations

Most studies evaluating the real-world effectiveness of GLP-1RA for weight loss are observational studies of the 'before-after' type, that is, comparing post-treatment initiation body weight with pre-treatment weight in people who all are exposed to the drug of interest. In total, we reviewed 24 studies[50–73] (Table 1), most of which were published recently, that is, in 2024.[50–64]

In general, many real-world studies suggested smaller weight loss (in kg or %) than what has been observed in the RCTs (i.e., up to 6% with liraglutide, 14% with semaglutide and 18% with tirzepatide vs. placebo).[74] Estimated weight loss was highly variable between studies; however, even within the same GLP-1RA, this was related to differences in user characteristics such as the proportion with T2D and previous use or not of GLP-1RA at baseline, differences in dosages of the drug, comprehensiveness of the weight management programme, follow-up time and weight measure used (e.g., self-reported or other measurements of body weight). The percentage weight reduction over typically 6–12 months of follow-up thus ranged from 2.2% to 18.5% for liraglutide,[52,55] 4.4% to 19.5% for semaglutide[61,65] and 4.8% to 21.2% for tirzepatide.[50,59] Importantly, the weight-loss effectiveness of GLP-1RA was similar to what has been observed in trials when focusing on the subgroup of adherent patients who consistently took their prescribed GLP-1RA, for example, at 12 months follow-up,[50,53,55–58,61] whereas studies reporting results in an 'as-started' approach found considerably lower effectiveness.[52,59,63,66] Semaglutide and tirzepatide initiators appeared to achieve the greatest weight loss in real life, and weight loss effects were weaker for patients with T2D than for obese people without diabetes,[52,58,65,67] which was also observed in trials.[18,75] Only two studies of tirzepatide for T2D were identified,[59,60] and they reported lower weight loss results than in the trials. Both studies included many individuals switching to tirzepatide from other GLP-1RAs, that is, individuals generally not included in the SURPASS and SURMOUNT-1 trials, with those switching from semaglutide seemingly experiencing further weight loss on tirzepatide treatment.

4.3 | Comparative effectiveness studies of GLP-1RA for weight loss

In general, there were few large, methodologically strong head-to-head comparative effectiveness studies of weight loss in obese users of different GLP-1RA for weight loss (Table 2). Liraglutide has been compared with dulaglutide,[76–78] showing no clear difference in weight loss. In patients receiving GLP-1RA treatment for T2D or obesity, semaglutide use was more likely to lead to weight reduction of ≥10% compared with liraglutide use.[52] In individuals without T2D, weight loss was 6.9% for semaglutide, 6.6% for liraglutide and 3.1% for dulaglutide.[82] A newer large real-world comparative cohort study from the US of more than 18 000 adults with overweight or obesity compared weight loss during treatment with semaglutide or tirzepatide.[79] The treatment was labelled for T2D, yet only 52% of individuals in the study were classified as having T2D. The achieved treatment doses were not reported. The study found a larger weight loss at 12 months for tirzepatide (−15.3%) versus semaglutide (−8.3%) in individuals who had not been excluded due to discontinuation or GLP-1RA switching.[79] Two recent studies based on the TriNetX database have compared users of tirzepatide with either users of semaglutide[81] or other GLP-1RAs (combined).[80] Anson et al. followed individuals after six months of completed treatment with tirzepatide and semaglutide and found that tirzepatide was associated with greater weight loss and decreased risk of developing T2D in individuals without pre-existing diabetes compared with semaglutide at one-year follow-up.[81] In patients with T2D, Chuang et al. found a greater effect on weight loss with tirzepatide than other GLP-1RA combined; however, treatment duration was not reported.[80] More well-conducted real-world studies in different cohorts and with comparable doses are required for concluding on real-world comparative effectiveness.

4.4 | Adverse effects of GLP-1RA in clinical practice

Although adverse effects with GLP-1RA use are frequent[21,83] and may lead to use of low doses or total discontinuation, real-world

TABLE 1 Observational studies on the clinical effectiveness of glucagon-like peptide-1 receptor agonist (GLP-1RA) for weight loss in real-world populations.

Clinical effectiveness, weight loss					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA-exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Population: Obesity without diabetes					
Drug in study: Liraglutide					
Talay et al., *Diabetes Obes Metab*, 2024[54]	Individuals initiating treatment in the Juniper weight-management program and receiving Liraglutide injection for weight loss between November 2021 and August 2023, Australia	Liraglutide-WL = 670 Mean age 44, 97% female, mean BMI 34, 0% T2D	Cohort, single-arm Individuals were required to complete two follow-up questionnaires (at 90–112 days and at 215–234 days)	No average time from program initiation to completion of first follow-up questionnaire reported	Weight loss (mean, %) on Liraglutide, persistent individuals: At 32 weeks: −11.6%
Population: Mixed					
Drug in study: Semaglutide					
Alabduljabbar et al., *Endocrine*, 2024[56]	Adults receiving semaglutide for weight loss in an obesity outpatient clinic, Electronic medical records, Ireland, July 2021–March 2023	Semaglutide-WL = 350 Mean age 48 years, 80% female, mean BMI 41, 8% T2D	Cohort, single-arm	6 months	Weight loss, mean (%), persistent individuals: At 3 months (n = 287): −6.6%, equivalent to −7.5 kg At 6 months (n = 224): −12%, equivalent to −13.6 kg
Ruseva et al., *Obes Sci Pract*, 2024[57]	Adults initiating semaglutide injection for weight loss between June 2021 and March 2022, across diverse practice settings and many health systems, Electronic Health Records, US	Semaglutide-WL = 343 Mean age 48 years, 85% female, mean BMI 38, 8% T2D	Cohort, single-arm Individuals had to be GLP-1RA naïve, and were required to have escalated to the 2.4 mg dose within 182 days from treatment initiation	6 months	Weight loss, mean (%): At 6 months: −10.0%, equivalent to −10.5 kg
Ghusn et al., *JAMA Netw Open*, 2022[67]	Adults initiating Semaglutide injection for weight loss at one referral centre for weight management, Mayo Clinic, US, electronic medical record database, 2021–2022	Semaglutide-WL = 175 Mean age 49 years, 75% female, mean BMI 41, 16% T2D	Cohort, single-arm Individuals were excluded if they were <3 months on semaglutide 56% reached low dose (1 mg or less), 44% high dose	6 months	Weight loss (mean), persistent individuals: At 3 months (n = 175): −5.9%, equivalent to −6.7 kg At 3 months, among subjects with T2D: −3.9% At 3 months, among subjects without T2D: −6.3% At 6 months (n = 102): −10.9%, equivalent to −12.3 kg At 6 months, among subjects with T2D: −7.2% At 6 months, among subjects without T2D: −11.8% Higher weight loss on high dose (−12.1%) vs. low dose (−9.2%)

TABLE 1 (Continued)

Clinical effectiveness, weight loss					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA-exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Ghusn et al., *Int J Obes (Lond)*, 2024[58]	Individuals prescribed Semaglutide injection for weight loss between January 2021 and January 2023, multi-centred, Electronic Medical Records, US	Semaglutide-WL = 304 Mean age 49 years, 73% female, mean BMI 41, 27% T2D	Cohort, single-arm Individuals were excluded if they had <3 months follow-up (<3 months on the medication), had bariatric procedures, or were taking another weight loss drug (with only liraglutide considered from the GLP-1RA group)	12 months	Weight loss, mean (%), persistent individuals: Among all subjects: At 3 months (n = 249): −5.7% At 6 months (n = 233): −9.7% At 9 months (n = 157): −12.7% At 12 months (n = 113): −13.4% Among subjects with T2D: At 3 months (n = 69): −4.5% At 6 months (n = 61): −7.6% At 9 months (n = 45): −9.9% At 12 months (n = 45): −9.8% Among subjects without T2D: At 3 months (n = 180): −6.2% At 6 months (n = 172): −10.5% At 9 months (n = 112): −13.8% At 12 months (n = 68): −15.8%
Mayer et al., *Diabetes Obes Metab*, 2024[51]	Adults initiating Semaglutide between 2018 and 2022, All of US Research Program (diverse clinical settings, multiple sites program), Electronic Health Records, US	Semaglutide, all indications = 3739 Semaglutide-injection = 3364 (semaglutide-T2D = 3154, semaglutide-WL = 210) semaglutide-oral = 435 Mean age 58 years, 62% female, mean BMI around 34 57% T2D and obesity, 17% T2D only, 16% obesity only (9% with unknown obesity/T2D status excluded from analyses)	Cohort, single-arm Outcome evaluated among individuals with obesity (with or without diabetes) who had available measurements for analysis	Mean time from drug initiation to last recorded date in electronic health records = 472 days	Weight loss (mean, %) at end of follow-up, regardless of follow-up time, regardless of discontinuation or not: All semaglutide: −4.7 kg Semaglutide-injection: −4.8 kg Semaglutide-oral: −3.6 kg
Powell et al., *Obesity (Silver Spring)*, 2023[65]	Individuals prescribed semaglutide injection for T2D, across 10 Health Systems, electronic health records, March 2017–April 2022	Semaglutide-T2D = 539 Mean age 56 years, 58% female, mean BMI 37, 83% T2D	Cohort, single-arm Individuals required to have at least 3 recorded prescriptions over 12 weeks and semaglutide exposure of at least 26 weeks	52 weeks	Weight loss (mean): At 52 weeks: −4.4%, equivalent to −4.8 kg At 52 weeks, among subjects with diabetes (n = 450): −3.9%, equivalent to −4.2 kg At 52 weeks, among individuals without diabetes (n = 85): 7.4%, equivalent to −7.9 kg
Talay et al., *Diabetes Obes Metab*, 2024[53]	Individuals initiating treatment in the Juniper weight-management program and receiving Semaglutide injection between April 2022 and April 2023, UK	Semaglutide injection = 1882 Mean age 45 years, 91% female, mean BMI 35, % T2D not clear, 6% pre-diabetes	Cohort, single-arm Individuals were required to complete the first follow-up questionnaire within 140–170 days after initiation, and to have a minimum of 6 semaglutide orders at that time	Average time from program initiation to completion of first follow-up questionnaire: 154 days	Weight loss (mean, %) on semaglutide, persistent individuals: At first questionnaire (approx 5 months): −10.7%

(Continues)

TABLE 1 (Continued)

Clinical effectiveness, weight loss					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA-exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Drug in study: Liraglutide					
Oral et al., *J Clin Med*, 2024[55]	Adults prescribed Liraglutide injection for weight loss between January 2022 and January 2024, tertiary private clinics from two hospitals, Turkey	Liraglutide-WL = 568 Mean age 42 years, 86% female, mean BMI 36, 8% T2D	Cohort, single arm Individuals were required to be on drug treatment for at least 4 weeks, to be without a previous history of GLP-1RA use, to not be on medication that affect weight loss, and to follow diet and exercise recommendations	24 weeks Very few followed for that time	Weight loss (mean, %) on liraglutide: At 4 weeks (n = 568): −6.6%, equivalent to −6.5 kg At 8 weeks (n = 210): −10.8%, equivalent to −10.7 kg At 12 weeks (n = 84): −15.0%, equivalent to −15.4 kg At 24 weeks (n = 40): −18.6%, equivalent to −19.0 kg
Park et al., *Int J Obes (Lond)*, 2021[68]	Individuals ≥17 years old initiating liraglutide injection for weight loss starting 2018, multi-centre, South Korea	Liraglutide-WL = 769 Mean age 45 years, 68% female, mean BMI 32, 37% T2D	Cohort, single-arm Individuals excluded if they had previous GLP-1RA intake; individuals required to have at least one visit within 6 months Mean daily dose 2.2 mg at 6 months	6 months	Weight loss (mean), persistent individuals: At 2 months (n = 672): 3.4%, equivalent to −2.9 kg At 4 months (n = 427): 4.8%, equivalent to −4.2 kg At 6 months (n = 219): 5.9%, equivalent to −5.1 kg At 6 months, among those without T2D (n = 108): −5.6 kg At 6 months, among those with T2D (n = 111): −4.7 kg
Suliman et al., *Diabetes Obes Metab*, 2019[71]	Individuals initiating Liraglutide for weight loss between January 2017 and April 2018 as part of routine care, multi-centre, UAE	Liraglutide-WL = 787 Mean age 39 years, 80% women, mean BMI 37, 55% T2D	Cohort, single-arm Individuals were required to have been dispensed liraglutide and received follow-up on at least one occasion	Median duration of treatment: 213 days (for individuals treated for ≥16 weeks); 296 days (for individuals treated for ≥28 weeks)	Weight loss (median): At end of follow-up, subjects treated for ≥16 weeks (n = 787): −6.4%, equivalent to −6.0 kg At end of follow-up, subjects treated for ≥28 weeks (n = 340): −7.6%, equivalent to −7.4 kg
Drug in study: more than one type					
Ard et al., *Obesity (Silver Spring)*, 2024[50]	Adults participating in the WeightWatcher telehealth program and initiating any weight loss drug between January 2022 and July 2023, US	Total users with 12 months follow-up and outcome data = 6089 Tirzepatide = 4700 Semaglutide-T2D = 195 Semaglutide-WL = 45 Liraglutide-WL = 162 Metformin = 858, few users of other drugs Mean age 43 years, 91% female, mean BMI 37, 3% T2D	Cohort, single-arm Analysis by first and last prescription type was performed at 12 months. Included individuals requested to have at least one prescription refill	Mean treatment duration in cohort with complete 12 months data = 12.6 months	Weight loss (mean, %) in persistent users with complete 12 months data: At 12 months, all drugs (n = 6089): 19.4% (equivalent to −20.2 kg) At 12 months, with first and last prescription tirzepatide: 21.2% At 12 months, with first and last prescription semaglutide-T2D: 13.8% At 12 months, with first and last prescription semaglutide-WL: 15.3% At 12 months, with first and last prescription liraglutide-WL: 12.0%

TABLE 1 (Continued)

Clinical effectiveness, weight loss					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA-exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Gasoyan et al., *JAMA Netw Open*, 2024[52]	Adults with BMI ≥ 30 initiating semaglutide injection or liraglutide injection between 2015 and 2022, Electronic Health Records from Ohio and Florida, US	Semaglutide or liraglutide injection, all indications = 3389 Semaglutide-T2D = 1341 Semaglutide-WL = 377 Liraglutide-T2D = 1444 Liraglutide-WL = 227 Mean age 50 years, 55% female, median BMI 38, 82% T2D as a treatment indication	Cohort, single-arm	12 months 4 in 10 patients had persistent medication coverage at 12 months; 46% semaglutide, 36% liraglutide	Weight loss (mean, %), irrespective of persistence: At 12 months, all subjects: 3.7% At 12 months, semaglutide: 5.1% At 12 months, liraglutide: 2.2% At 12 months, semaglutide or liraglutide for T2D: 3.2% At 12 months, semaglutide or liraglutide for obesity: 5.9% Weight loss (mean, %) in individuals with persistent drug coverage: At 12 months, all subjects ($n = 1381$): −5.5% At 12 months, liraglutide-WL: −5.6% At 12 months, liraglutide-T2D: −3.1% At 12 months, semaglutide-WL: −12.9% At 12 months, semaglutide-T2D: −5.9% Weight loss (mean, %) in individuals with 90–275 coverage days: At 12 months, all subjects ($n = 1254$): −2.8% At 12 months, liraglutide-WL: −3.4% At 12 months, liraglutide-T2D: −1.7% At 12 months, semaglutide-WL: −5.2% At 12 months, semaglutide-T2D: −3.6% Weight loss (mean, %) in individuals with <90 coverage days: At 12 months, all subjects ($n = 754$): −1.8% At 12 months, liraglutide-WL: −0.8% At 12 months, liraglutide-T2D: −1.2% At 12 months, semaglutide-WL: −3.7% At 12 months, semaglutide-T2D: −2.0% Semaglutide associated with ≥10% weight loss compared with liraglutide (adjusted OR 2.19 [95% CI, 1.77–2.72])
Population: With T2D					
Drug in study: Tirzepatide					
Buckley et al., *Diabetes Obes Metab*, 2024[59]	Individuals with T2D initiating Tirzepatide between October 2022 and December 2023, clinical data in a specialist outpatient diabetes centre (single centre), UAE	Tirzepatide = 3686 Mean age 54 years, 59% female, mean BMI 35 kg/m^2, all had T2D	Cohort, single-arm Tirzepatide mean dose at 40 weeks: 8.8 mg/week; 14% reached maximum dose of 15 mg/week. 20% discontinued treatment	40 weeks (+/− 4 weeks)	Weight loss, mean: (%): At 40 weeks, intention-to-treat ($n = 3686$): −4.8%, equivalent to −4.5 kg (6.9 kg) At 40 weeks, among continuers ($n = 2962$): −5.6%, equivalent to −5.3 kg (6.9 kg) At 40 weeks, among discontinuers ($n = 724$): −1.5%, equivalent to −1.5 kg (6.2 kg) Weight loss dose-dependent, and highest in GLP-1RA naïve individuals

(Continues)

TABLE 1 (Continued)

Clinical effectiveness, weight loss					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA-exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Kelly et al., *Diabetes Obes Metab*, 2024[60]	Adults with T2D treated with Tirzepatide between June 2022 and October 2023, urban academic health centre, electronic medical records, US	Tirzepatide = 570 evaluated for weight outcome Mean age 55 years, 52% women, mean BMI 34 kg/m^2, all had T2D	Cohort, single-arm Individuals were required to have had at least 3 months of continuous Tirzepatide Most recent dose was 8.8 mg/week; 13% reached maximum dose of 15 mg/week	Median = 10.4 months	Weight loss, mean (%), persistent individuals (n = 570): At end of study: −6.5%, equivalent to −7.3 kg Highest weight loss in GLP-1RA naïve (9.0 kg) vs. 6.0 kg in switchers
Drug in study: Semaglutide					
Alsheikh et al., *Diabetes Ther*, 2024[61]	Adults with uncontrolled T2D treated with Semaglutide, chart review of records between April 2020 and April 2023, multicenter, Saudi Arabia	Semaglutide = 1223 Semaglutide-T2D = 80% Semaglutide-oral = 20% Mean age 54 years, 51% female, mean BMI 39, all had T2D	Cohort, single-arm Individuals were required to have used semaglutide for at least 6 months At 12 months, 80% had reached 1 mg or equivalent	12 months	Weight loss, mean (%), persistent individuals: At 6 months: −13.0%, equivalent to −14.9 kg At 12 months: −19.6%, equivalent to −22.6 kg No outcome difference observed for naïve (∼80%) or non-naïve to previous GLP-1RA
Caballero Mateos et al., *Nutrients*, 2024[62]	Adults initiating Semaglutide injection for T2D treatment between June 2019 and July 2020, medical records, 10 tertiary hospitals in Spain	Semaglutide-T2D = 752 Mean age 61, 47% female, mean BMI 37, all had T2D	Cohort, single-arm Individuals required to have been on treatment for at least 6 months before inclusion into the study At 12 months, the majority of patients had reached 1 mg	12 months	Weight loss, mean: At 6 months (n = 686): −7.0 kg At 12 months (n = 472): −9.2 kg
Rudofsky et al., *Adv Ther*, 2024[63]	Adults in routine clinical practice who switched to semaglutide injection for T2D from another GLP-1RA, pooled SURE studies across 10 countries	Semaglutide-T2D = 651 Mean age 60 years, 47% female, mean BMI 35, all had T2D	Cohort, single-arm Post hoc analysis of studies in the SURE program	Around 30 weeks	Weight loss, mean, irrespective of persistence: At 30 weeks: −3.7 kg
Yale et al., *BMJ Open Diabetes Res Care*, 2022[66]	Adults initiating semaglutide injection for T2D, pooled SURE studies from Canada, Denmark/Sweden, Switzerland, and the United Kingdom, March 2018–August 2020	Semaglutide-T2D = 1212 Mean age 60 years, 39% female, mean BMI 35, all had T2D	Cohort, single-arm Post hoc analysis of studies in the SURE program Mean dose at end of study 0.8 mg	Around 30 weeks	Weight loss (mean), irrespective of persistence: At around 30 weeks: −4.7 kg
Lingvay et al., *Diabetes Ther*, 2021[69]	Adults switching to semaglutide injection for T2D from another GLP-1RA, Electronic Health Records, EXPERT study, US, January 2018–April 2020	Semaglutide-T2D = 921 Mean age 58 years, 57% female, mean BMI 37, All had T2D	Cohort, single-arm	12 months	Weight loss (mean): At 6 months (n = 921): −2.1 kg At 12 months (n = 532): −2.8 kg

TABLE 1 (Continued)

Clinical effectiveness, weight loss					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA-exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Brown et al., *Diabetes Obes Metab*, 2020[70]	Adults initiating semaglutide injection for T2D between February 2018 and February 2019 in a specialist endocrinology practice, SPARE study, LMC Diabetes Registry, multicenter, Canada	Semaglutide-T2D = 937 Mean age 57 years, 40% women, all had T2D	Cohort, single-arm Individuals were excluded if they had a previous history of GLP-1RA use; individuals were required to maintain therapy during follow-up	3- to 6-months follow-up (+/− 6 weeks) Mean follow-up 4.9 months	Weight loss (mean), persistent individuals: At 3- to 6- months follow-up: −3.9 kg Greater weight reduction reported with 1.0 mg than with lower doses
Drug in study: Liraglutide					
Butt et al., *J Pharm Policy Pract*, 2024[64]	Individuals initiating Liraglutide injection for T2D, electronic clinical records, multicenter, Pakistan, March 2016–November 2021	Liraglutide-T2D = 624 Mean age 43 years, 52% female, mean BMI 34, all had T2D	Cohort, single-arm Individuals excluded if they were on concurrent GLP-1RA therapy: and had to have at least 12 months follow-up availability in the electronic clinical records	24 months	Weight loss (mean): At 6 months (n = 589): −5.1 kg At 12 months (n = 413): −3.8 kg At 18 months (n = 397): −4.0 kg At 24 months (n = 379): −7.5 kg
Mata-Cases et al., *Curr Med Res Opin*, 2019[72]	Adults initiating GLP-1RA treatment (liraglutide, llixisenatide, exenatide) between 2007 and 2014 in primary health care, multicenter, Spain	Total of 4242 patients; Liraglutide-T2D = 2504 Median age 59 years, 50% female, mean BMI 38, all had T2D	Cohort study The analyses were performed for GLP-1RA as a group and by GLP-1RA type	6–12 months of treatment	Weight loss (mean): at end of follow-up, among all GLP-1RA: −3.6 kg At end of follow-up, among liraglutide initiators: −4.0 kg
Lapolla et al., *Adv Ther*, 2018[73]	Adults initiating liraglutide injection for T2D in 2011 in daily practice, multicenter, ReaL study, Italy	Liraglutide-T2D = 1723 Mean age 59 years, 45% female, mean BMI 36, All had T2D	Cohort, single-arm Treatment discontinuation during the 24 months study period did not represent a reason for exclusion	24 months *N* with available data at 24 months: 1217 (95.4% of which had weight info)	Weight loss (median), irrespective of persistence: At 4 months: −2.8 kg At 12 months: −3.3 kg At 24 months: −3.4 kg

Abbreviations: BMI, body mass index; CI, confidence interval; T2D, type 2 diabetes.

TABLE 2 Comparative effectiveness of different glucagon-like peptide-1 receptor agonists (GLP-1RAs) for weight loss in real-world populations.

Comparative effectiveness, weight loss					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA-exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Chang et al., *Cardiovasc Diabetol*, 2020[76]	Patients with T2D followed at seven medical institutes in Taiwan, 2016–2018, linked EMR data	Liraglutide = 1513 Dulaglutide = 1512 Propensity score-matched population ($n = 1966$): mean age 57 years, 52% female, average weight 78 kg	Multicenter comparative cohort study using propensity score balancing	12 months	Weight reduction (kg): At 12 months: Liraglutide −1.6 kg At 12 months: Dulaglutide −1.1 kg
Morieri et al., *Metabolism*, 2020[77]	Patients with T2D treated between 2010 and 2018. Italy	Dulaglutide: $n = 849$ Liraglutide: $n = 1371$ Exenatide: $n = 198$	Retrospective multicenter cohort study using propensity score matching.	5.9 months (average)	No difference in weight loss
Giorgino et al., *Diabetes Obes Metab*, 2023[78]	Patients with T2D initiating treatment between 2017 and 2019 in France, Germany and Italy	Dulaglutide: $n = 1014$ Liraglutide: $n = 991$	Prospective, observational study	24 months	No difference in weight loss.
Gasoyan et al., *JAMA Netw Open*, 2024[52]	Adults with BMI ≥ 30 initiating treatment between 2015 and 2022 Electronic health records from Ohio and Florida	All: $n = 3389$ Semaglutide-T2D: $n = 1341$ Semaglutide-WL: $n = 377$ Liraglutide-T2D: $n = 1444$ Liraglutide-WL: $n = 227$	Retrospective cohort study Outcomes: Weight change (percentage) and weight reduction ≥10%	12 months	Weight loss (%): At 12 months: Semaglutide −5.1% At 12 months: Liraglutide −2.2% Semaglutide positively associated with ≥10% weight loss compared with liraglutide (adjusted OR 2.19 [95%CI 1.77–2.72])
Rodriguez et al., *JAMA Int Med*, 2024[79]	Adults with overweight or obesity (BMI ≥ 27) who initiated semaglutide or tirzepatide labelled for T2D (regardless of T2D among individuals). Linked EMR data from US health care systems, 2022–2023	Semaglutide-T2D 0.5 mg ($n = 9192$) Tirzepatide-T2D 5.0 mg ($n = 9193$) In the propensity score-matched population ($n = 18\,386$) mean age was 52 years, 71% were female, mean was BMI 39.1% and 52% had T2D	Comparative cohort study of propensity-score-matched semaglutide and tirzepatide initiators. Multiple imputations were used for weight values Outcome evaluated in individuals still on treatment (patients were censored from analysis if discontinuation) Treatment doses unclear (assumed target dose according to brand dose at T2D indication)	12 months	Mean weight loss (%): At 3 months: Tirzepatide −5.9% At 3 months: semaglutide −3.6% At 6 months: Tirzepatide −10.1% At 6 months: Semaglutide −5.8% At 12 months: Tirzepatide −15.3% At 12 months: Semaglutide −8.3%
Chuang et al., *JAMA Netw Open*, 2024[80]	Adults with T2D and treatment initiation between 2022 and 2023. TriNetX database (US patients)	Tirzepatide: $n = 14\,834$ Other GLP-1RA: $n = 125\,474$ After propensity score matching, $n = 14\,832$ in each treatment group (no information on amount of each GLP-1RA)	Comparative study of propensity score matched tirzepatide or other GLP-1RA (combined) users	10.5 months (median)	Treatment differences (kg): Greater with tirzepatide −2.9 kg (95%CI −4.8; −1.1) compared with other GLP-1RA (combined)

TABLE 2 (Continued)

Comparative effectiveness, weight loss					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA-exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Anson et al., *EClinicalMedicine*, 2024[81]	Adults ≥18 years without T2D and six months of treatment with GLP-1-RA without T2D (cohort 1) or Adults ≥18 years with T2D (cohort 2) TriNetX database	Cohort 1 (without T2D): Tirzepatide: $n = 6928$ Semaglutide: $n = 46\,458$ After propensity score matching $n = 6923$ in each group Cohort 2 (with T2D): Tirzepatide: $n = 4225$ Semaglutide: $n = 46\,231$ After propensity score matching $n = 4223$ in each group	Propensity-score-matched individuals in two cohorts (with and without T2D)	12 months after the defined index event (6 months of tirzepatide or semaglutide)	Cohort 1 (without pre-existing T2D): Weight loss: At 12 months: Tirzepatide −7.7 kg At 12 months: Semaglutide −4.8 kg Cohort 2 (patients with T2D): Weight outcomes not reported
Huang et al., *Diabetes Obes Metab*, 2024[82]	Individuals with obesity (BMI ≥30) and without T2D identified through TriNetX Global Network from 2016 to 2024	Total cohort of 3 729 925 individuals with obesity After propensity score-matching: GLP-1 RA: $n = 12\,123$; no glucose-lowering medication: $n = 12\,123$ GLP-1RA: Semaglutide: $n = 7457$ (semaglutide-T2D $n = 3100$, semaglutide-WL $n = 4079$, semaglutide-oral $n = 278$) liraglutide $n = 2382$ (liraglutide-T2D $n = 938$, liraglutide-WL $n = 144$) Exenatide $n = 20$ Dulaglutide $n = 710$	Cohort study using propensity-score-matching	5 years after index event (six consecutive months of GLP-1RA use) Average duration of GLP-1RA use was 168 days	Weight loss (%): Semaglutide: −6.9% Liraglutide: −6.6% Dulaglutide: −3.1%

Abbreviations: BMI, body mass index; CI, confidence interval; EMR, electronic medical record; T2D, type 2 diabetes.

evidence on when adverse effects lead to such outcomes in clinical practice is limited.[20,21] Further, the long-term safety of weight loss medications is not well understood, as weight loss RCTs have been relatively short (typical timespan 1–2 years) and too small to detect more rare adverse events with any certainty. As GLP-1RAs have been used to treat T2D for more than 15 years (although for a different population and usually in lower doses than for weight loss), real-world studies of T2D populations can offer some insight for weight-loss populations as well. Here, we summarise the available evidence on frequently reported and/or severe adverse events for GLP-1RA use,[83] focusing on newer large real-world population studies including GLP-1RA users with either obesity or T2D.

4.4.1 | Gastrointestinal disturbances

GLP-1RA has numerous effects on the gastrointestinal tract and nervous system, including slowing gastric emptying, regulating appetite and nausea in the brainstem and hypothalamus, and affecting gut motility and secretion.[84] Accordingly, in both RCTs and in adverse event reporting databases, mild to moderate gastrointestinal disturbances have been frequent, primarily nausea, abdominal pain, gastrointestinal reflux, bloating, vomiting, diarrhoea and constipation,[21,85] occurring in approximately 80% of GLP-1RA treated patients across all major weight loss RCTs.[17,19,25,74] In a meta-analysis of 76 RCTs in T2D, liraglutide, semaglutide and tirzepatide were all associated with significantly increased ORs of nausea, vomiting and diarrhoea.[27] The occurrence of such gastrointestinal side effects increases with the dose used.[86,87]

Comparable real-world data are scarce, as mild to moderate gastrointestinal symptoms do not necessarily lead to healthcare contacts or registration in medical records or databases. In a community pharmacy-based survey of semaglutide users, six in 10 users reported having experienced side effects, most commonly nausea (35%) and constipation (29%),[88] suggesting a similar occurrence of these symptoms in clinical practice as in RCTs. Clinical practice experience implies that the symptoms are often dose dependent, observed during the dose escalation period, and tend to diminish over time with continued use.[79,84,89]

4.4.2 | Gastroparesis and intestinal obstruction

Severe gastrointestinal symptoms, including gastroparesis and intestinal obstruction/ileus, have been anecdotally reported with GLP-1RA use, with a pharmacovigilance signal for intestinal obstruction seen in WHO's VigiBase.[90] These signals have not generally been observed in RCTs[74] and there is currently sparse real-world evidence existing from large epidemiological studies. A recent real-world study of people with obesity compared initiators of semaglutide and liraglutide to those initiating bupropion-naltrexone and found markedly increased rates of bowel obstruction (hazard ratio [HR] 4.22; 95% confidence interval [CI] 1.02–17.40) and gastroparesis (3.67 [95% CI, 1.15–11.90]).[91] However, this study has been criticized for methodological shortcomings.[92] The American Society of Anesthesiologists (ASA)[93] has, however, made recommendations to hold GLP-1RA medications on the day of surgical procedures for daily users and a week prior to an elective procedure for weekly users to reduce the risk of gastroparesis.[84]

4.4.3 | Gallbladder/biliary disease

A meta-analysis from 2022 of 76 RCTs involving 103 371 patients starting GLP-1RA drugs for either T2D or weight loss, compared with placebo or non-GLP-1RA drugs, found a modestly elevated RR of 1.37 (95% CI 1.23–1.52) for gallbladder or biliary disease.[94] These risks seem dose dependent and there were higher risk estimates in RCTs for weight loss (RR 2.29; 95% CI 1.64–3.18) than for T2D (RR 1.27; 95% CI, 1.14–1.43).[95] A meta-analysis of tirzepatide found an increased risk (albeit statistically imprecise) for gallbladder or biliary disease with this particular GLP-1RA compared with the use of other GLP-1RAs (RR 1.94; 95% CI 0.58–6.47).[96] A real-world study also found increased risks of biliary disease with any GLP-1RA use compared with bupropion-naltrexone (HR 1.5; 95% CI 0.9–2.5).[91] A larger real-world comparative cohort study of initiators of semaglutide and tirzepatide for overweight found no differences in risks of cholecystitis and cholelithiasis between these two drugs.[79] Of note, the risk increase of developing gall stones is related to the magnitude of any weight loss in general, and, for example, bariatric surgery is associated with a substantially increased risk of subsequent gallbladder or biliary disease.[95]

4.4.4 | Pancreatitis and pancreatic cancer

A meta-analysis of 11 cardiovascular outcome trials involving patients with T2D starting GLP-1RA drugs found no materially elevated risk of acute pancreatitis (rate ratio 1.05; 95% CI 0.78–1.41) or pancreatic cancer (rate ratio 1.14 [0.77–1.70]).[97] Another meta-analysis of 43 RCTs of different GLP-1RAs for T2D found an OR of 1.24 (0.94–1.64) for pancreatitis and OR 1.28 (0.87–1.89) for pancreatic cancer.[98] The absence of any strong association with pancreatitis for GLP-1RAs has been corroborated by numerous large real-world observational studies of patients with T2D already a decade ago.[99,100] Newer registry-based T2D cohort studies have suggested a decreased risk of most obesity-associated cancers in patients with T2D using GLP-1RA, including decreased risks of pancreatic cancer among a US study (HR 0.41, 0.33–0.50)[101] and Israel (HR 0.50, 0.15–1.71).[102]

In populations using GLP-1 RAs in higher doses specifically for weight loss, less is currently known about pancreatitis and pancreatic cancer risks.[79,91] A real-world comparative cohort study found rates of pancreatitis of 4.6 (semaglutide) and 7.9 (liraglutide) per 1000 person-years compared with a remarkably low rate of 1.0 in bupropion-naltrexone initiators, yielding a high yet imprecise HR of 9.1 (95% CI 1.3–66.0).[91] Another real-world comparative cohort study of GLP-1RA initiators for overweight found no difference between these semaglutide and tirzepatide (HR 1.04, 0.52–2.11).[79] These real-world pancreatitis rates of approximately 4 to 8 per 1000 person-years with GLP-1RA are several fold higher than in the major weight loss RCTs of liraglutide RCT.[17–19,26] Of note, meta-analyses of RCTs in either T2D or weight loss have found no increased risk of pancreatitis.[74,103] However, in the RCTs, people were not eligible if they had a history of chronic or recent acute pancreatitis, and if they had any disorder (such as psychiatric illness or alcohol abuse) potentially compromising their trial compliance, which—together with more selective pancreatitis case adjudication in the trials—might explain the higher absolute pancreatitis risks in some real-world studies. Although most clinical guidelines as well as EMA and FDA list pancreatitis as a possible side effect of GLP-1RAs, most real-world studies suggest no clear increased pancreatitis risk with GLP-1RAs, thus corroborating findings from meta-analyses of the RCTs.

4.4.5 | Thyroid cancer and other disorders

Treatment with liraglutide or exenatide has been associated with thyroid C-cell proliferation and the formation of thyroid C-cell tumours in rodents,[104] although the relevance to humans is uncertain. Therefore, the FDA lists individual or family history of medullary thyroid carcinoma (MTC) as well as multiple endocrine neoplasia syndrome type 2 (MEN2) as contraindications to the use of GLP-1RA. Of note, the EMA has not included this in the European licensing of these drugs. A meta-analysis of 45 RCTs including 94 063 participants treated with GLP-1RAs for either glucose-lowering or weight reduction found a weak association of GLP-1RAs with any type of thyroid disorder overall (RR 1.28, 1.03–1.60), seemingly driven by liraglutide (1.37, 1.01–1.86) and dulaglutide (1.96, 1.11–3.45).[105] The RR for any thyroid disorders was 1.32 (1.05–1.66) in T2D trials whereas it was close to unity (0.91, 0.33–2.51) in weight loss trials. The overall GLP-1RA RR for thyroid cancer was 1.30 (0.86–1.97).[105] A recent Scandinavian real-world study[106] found no increased risk of thyroid cancer among initiators of GLP-1RA vs. dipeptidyl-peptidase 4 inhibitors (DPP4i). Another multinational real-world study of GLP-1RA initiators corroborated this with a pooled weighted HR 0.81 (CI 0.59–1.12).[107] Thus, most available evidence, both from trials and real-world settings,

suggests that any association between GLP-1RAs and thyroid cancer is either weak or non-existent.

4.4.6 | Depression and suicidality

Obesity and T2D per se are associated with depression,[108] with GLP-1RA showing protective effects against neuroinflammation in animal models that may in theory reduce depression risk.[109] Substantial weight loss can improve mental wellbeing but may also demask unresolved psychological issues.[110] Both weight loss drugs and bariatric surgery have been linked to a potentially increased risk of thoughts of self-harm and suicide,[111] with the EMA investigating numerous spontaneous reports in 2023.[112] A recent systematic review of real-world studies investigating the risk of depression in people with T2D using GLP-1RAs found no clear evidence of such an association, with most relative risk estimates close to 1.0.[109] Two newer large active-comparator new-user studies corroborated the absence of association with suicidal ideation and behaviours, suicide death, or self-harm, with adjusted HRs for GLP-1RA versus SGLT2i close to unity.[112,113]

4.4.7 | Eye disease

The SUSTAIN-6 trial of semaglutide for T2D suggested a potential link of this GLP-1RA with worsening diabetic retinopathy,[114] which was not observed in, for example, the liraglutide or dulaglutide trials.[115] Later subgroup and mediation analyses suggested that the majority of the effect might be attributed to a large and rapid glycated haemoglobin (HbA1c) reduction, a recognized risk factor for early worsening of diabetic retinopathy,[116] especially among patients with high HbA1c and baseline signs of retinopathy.[117] Several large real-world studies have examined the association between GLP-1RA and retinopathy, with apparently conflicting results in three recent large cohort studies,[115,118,119] leaving the question unsettled. Recent anecdotal evidence also suggests that semaglutide may be associated with an increased risk of non-arteritic anterior ischemic optic neuropathy (NAION), a rare but important cause of blindness in adults.[120] This was suggested in a study of selected patients evaluated by neuro-ophthalmologists at one academic institution (with a remarkably high occurrence of NAION overall),[120] and just recently corroborated in two large studies from Scandinavia finding a more than doubled risk of NAION with GLP-1RA use in T2D.[121,122] More research is needed to fully understand the relationship between GLP-1RAs and eye diseases.

5 | FUTURE REAL-WORLD RESEARCH DIRECTIONS

As evident above, there are numerous unmet research needs within the real-world space for use of GLP-1RA for weight loss. Here, we summarise 10 selected areas that we consider of particular importance for further studies.

5.1 | Overall drug utilization

With the rapid shift in treatment patterns, there is a need for continuously updated population-based drug utilization data, including key aspects such as costs and treatment persistence. The mapping of real-world users' characteristics to those of patients included in the phase III trials will help identify shifts in patient population and potentially explain different real-world effects. Finally, the use of doses lower than those tested in the trials[28,37] should be monitored.

5.2 | Responders

While the persistence to the use of GLP-1RAs does not seem worse compared with many other drugs, a substantial proportion cease treatment early on.[29–31,35] There is a need to understand what specific patient characteristics or subgroups drive such early discontinuation and to what extent (and for which patients) it is caused by lack of tolerability or lack of effect.

5.3 | Real-world effects

While the GLP-1RA is generally accepted to be highly efficacious in selected trial settings, there are multiple reasons why effect sizes could be expected in the real-world setting as discussed above, including the use of lower doses and differences in patient characteristics. Thus, the real-world weight-lowering effect and the cardiovascular and renal benefits documented in clinical trials[123–125] should be studied not only for the use of the drugs as intended in the trials and for similar patients, but also for effects in groups not included in the trials and with the use of lower doses.

5.4 | Comparative effects

Our review showed that most real-world studies have studied individual GLP-1RAs (Table 1), and only a few have performed comparative effectiveness or safety assessments (Table 2). Direct comparisons will be essential as they not only provide information of higher clinical relevance but also support more solid evidence, as the use of active comparators will likely reduce confounding in the assessment of both the efficacy and safety of these drugs.

5.5 | Other effects

Outside the main effects on weight and cardiovascular and kidney risks, there is a need to study additional clinical effects of GLP-1RA

use for weight management. This includes a continuum of secondary effects ranging from those that can be tied directly to the drugs' weight-lowering properties, such as reduction in the use of analgesics for arthritis or in the use of antifungals for infections, over less specific effects, such as changes in healthcare utilisation or use of psychotropics, to possibly true pleiotropic effects, for example, in the prevention of cancer or dementia.

5.6 | Cost-effectiveness

Considering the substantial cost of using GLP-1RA for weight management, there is a need to investigate the cost-effectiveness of these drugs regarding endpoints such as cardiovascular events and total mortality. Current, although sparse, real-world evidence suggests very high costs per prevented event in the total population,[126] pointing to a specific need to map cost-effectiveness across various patient subgroups.

5.7 | Effects of stopping

With many patients having achieved their desired weight loss using GLP-1RAs, there is an urgent need to study the effects of stopping treatment. Current evidence from trials suggests that weight is regained rapidly for patients who discontinue GLP-1RA treatment,[127–129] and worryingly, a substantial part of this regain seems to be fat mass.[130] However, the clinical relevance of this finding, with patients blinded to whether they received continued treatment or placebo, is very limited, as it mimics neither the situation nor the way in which treatment is stopped in clinical practice. Thus, real-world studies on the effects of stopping GLP-1RA treatment after having achieved a significant weight loss, as well as those of alternatives such as dose reduction or spacing, are needed.[131]

5.8 | Adverse events in obesity

As our review shows (Table 3), our knowledge on adverse events for the GLP-1RAs is largely based on the study of these drugs in the management of diabetes. There are several reasons why data on adverse events might not translate between these populations. For one, the users of GLP-1RAs for weight management are roughly 20–25 years younger on average than those using the same drugs for the management of diabetes. Even under the strong assumption that the relative risk increases translate between these populations, the much lower baseline risk of most diseases among younger individuals will make the absolute magnitude of such risks markedly different. Second, some adverse effects might be directly or indirectly linked to the indication of diabetes and hyperglycaemia. This is obvious for diabetic retinopathy, and also hypothesized for the use of GLP-1RA and risk of NAION, making it uncertain whether the same effect can be expected with the use of the drugs for weight management. As such, there is a need to study the occurrence of adverse effects specifically among users of GLP-1RA for weight management and in particular the absolute risk of these effects.

5.9 | Methodological quality

With the growing body of literature on the real-world use and effects of GLP-1RA, there is an increasing need to not only summarise this literature but also to evaluate and strengthen its methodological quality. Areas of particular focus are how to avoid selection bias, which is a frequent concern in studies that only include 'drug survivors',[53,55,58,60–62,65,67,70,71] that is, those retaining treatment over a prolonged period, or those restricting their analyses to high-dose users.[57]

5.10 | Data availability

The many real-world data sources available have their individual strengths and limitations. The identification of which data sources can be used to answer what research questions is central. For example, in most data sources, the general use of drugs other than GLP-1RA for obesity is limited, rendering the use of active comparators outside this drug class in the study of GLP-1RA effects difficult. However, some settings do have such use, for example, in Norway with a considerable use of naloxone/bupropion.[24] Another key problem is that many real-world data sources hold limited or no information on anthropometric measures including body weight or height, which precludes the direct assessment of real-world efficacy on weight or BMI. Such information is, however, available in data sources such as the Clinical Practice Research Datalink (CPRD) database in the United Kingdom, and in population surveys that can be linked with other health registries, in Scandinavia for example the Trøndelag Health Study,[136] the Danish Health and Morbidity surveys,[137] and the Better Health in Late Life cohort.[138] Further, several other factors will influence weight loss (i.e., physical activity, diet, smoking, alcohol intake, health literacy) and data on these parameters is rarely available in real-world studies, which may lead to uncontrolled confounding.

6 | CONCLUSIONS

Real-world evidence supports the effectiveness of GLP-1RA for weight loss, but the observed weight reduction in therapy initiators overall tends to be lower than in randomised controlled trials, likely due to lower adherence, persistence and the use of reduced doses in clinical practice. Semaglutide and tirzepatide starters appear to achieve the greatest weight loss, with emerging data suggesting that real-world outcomes may approach those seen in trials among highly adherent patients. Adverse events, particularly gastrointestinal disturbances, frequently lead to discontinuation, but otherwise, real-world data provide little evidence for severe adverse effects. Adverse events in the

TABLE 3 Comparative safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in selected large real-world population studies.

Comparative safety (adverse effects)					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Sodhi et al., *JAMA*, 2023[91]	New users of semaglutide or bupropion-naltrexone who had an obesity code around cohort entry, US, health claims database (IQVIA), 2006–2020	Liraglutide any type = 5411 Semaglutide any type = 613 Bupropion-naltrexone (*n* = 654) Mean age 51–54 years, 39%–44% female, no data on BMI	Comparative cohort study of initiators of semaglutide or liraglutide versus bupropion-naltrexon Specific gastrointestinal adverse events as outcomes Adjustment in Cox model for demographics, lifestyle, recent surgery (not BMI)	Follow-up to end of study period (2020) with censoring if switch, median follow-up 0.6 to 1.7 years varying by drug	Semaglutide/liraglutide versus bupropion-naltrexone gastrointestinal event rates per 1000: Biliary disease HR 1.50 (CI 0.89–2.53), rates 11.7/18.6 vs. 12.6 Pancreatitis HR 9.09 (CI 1.25–66.0), rates 4.6/7.9 vs. 1.0 Bowel obstruction HR 4.22 (CI 1.02–17.40), rates 0/8.1 vs. 1.7 Gastroparesis HR 3.67 (CI 1.15–11.90), rates 9.1/7.3 vs. 3.1
Rodriguez et al., *JAMA Int Med*, 2024[79]	Adults with overweight or obesity (BMI ≥ 27) who initiated semaglutide or tirzepatide labelled for T2D, linked electronic medical record data from US health care systems, 2022–2023	Semaglutide 0.5 mg = 9192 Tirzepatide 5.0 mg = 9193 PS-matched population = *N* = 18 386: mean age 52 years, 71% female, mean BMI 39, 52% T2D	Comparative cohort study of propensity-score-matched semaglutide and tirzepatide initiators Severe gastrointestinal adverse event (%) as outcome Adjustment for demographics, comorbidity, drugs, surgery, T2D, baseline weight	Follow-up on-treatment until discontinuation or administrative censoring, median follow-up 129 days	Tirzepatide vs. semaglutide severe gastrointestinal event rates per 1000: Bowel obstruction 6.3 vs. 5.5 (HR 1.12, CI 0.63–1.97) Cholecystitis 6.5 vs. 5.1 (HR 1.25, 0.70–2.21) Cholelithiasis 11.9 vs. 12.7 (HR 0.94, 0.36–1.39) Gastroenteritis 19.8 vs. 20.2 (HR 1.00, 0.73–1.37) Gastroparesis 3.6 vs. 4.8 (HR 0.73, 0.38–1.42) Pancreatitis 3.8 vs. 3.6 (HR 1.04, 0.52–2.11)
Pasternak et al., *BMJ*, 2024[106]	Adults (almost all with T2D) who initiated GLP-1RA vs. DPP4i inhibitors, nationwide register data in Denmark, Norway, and Sweden, 2007–2021	Any GLP-1RA = 145 410 (liraglutide 57%, semaglutide 33%, dulaglutide 5%, others 5%) Any DPP4i = 291 667 PS-weighted population: mean age 58 years, 47% female, 68% metformin, 30% insulin, no data on BMI	Active-comparator new-user cohort study with propensity score stratification Thyroid cancer as outcome Adjustment for sociodemography, comorbidity, drugs, markers of healthcare use (not BMI)	Mean follow-up 1.1 to 9.1 years, varying by specific drug	Thyroid cancer incidence GLP-1RA vs. DPP4i: HR 0.93 (0.66 to 1.31) Rates 0.13 in GLP-1RA and 0.15 in DPP4i per 1000 person years
Baxter et al., *Thyrorid*, 2025[107]	Adults with metformin use/T2D who initiated GLP1-RA or DPP4i, six population-based databases from Canada (Ontario), Denmark, Norway, South Korea, Sweden, Taiwan, 2007–2023	Any GLP1-RA = 98 147 DPP4i = 2 488 303	Multinational cohort study with PS weighting using standardized mortality ratio (SMR) weights Thyroid cancer as outcome Adjustment for demographics, comorbidity, co-medications	Median follow-up 1.8 to 3.0 years	Thyroid cancer: Pooled weighted HR 0.81 (CI 0.59–1.12), crude rates 0.18 in GLP-1RA and 0.59 in DPP4i per 1000 person-years
Cooper et al., *J*	Patients with T2D included in 4 separate studies from United Kingdom (CPRD),	Any GLP-1RA = between 501 and 34 587 exposed	A systematic review of 4 observational studies (2 cohort, 2	Follow-up varying from, 1 to 10 years across studies	UK (CPRD)[132]: incidence rate of depression or self-harm slightly higher for GLP-1RAs vs. SUs

(Continues)

TABLE 3 (Continued)

Comparative safety (adverse effects)					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Psychiatric Res, 2023[109]	Taiwan (national insurance database), and Denmark (2 studies, national registries)	people Mean age 50–57 years, 38%–45% women	case–control) examining association of GLP-1RA use with incident depression in patients with diabetes Various regression analyses for confounder adjustment		(aHR 1.25, CI 0.63–2.50), TZDs (aHR 1.18, CI 0.53–2.65), insulin (aHR 1.07, CI 0.39–2.94) Taiwan[133]: incidence of anxiety and/or depression was lower in GLP-1RAs than in non-users (aHR 0.80, CI 0.67–0.95), yet similar for depression only (aHR 0.94, CI 0.72–1.23) Denmark 1[134]: Exenatide aOR 0.93 (CI 0.75–1.15), liraglutide aOR 1.10 (CI 1.00–1.21), for depression diagnosis or antidepressant use Denmark 2[135]: aORs for any GLP-1RA and depression diagnosis/antidepressant: 0–0.2 DDD, 0.85 (CI 0.74–0.97); 0.2–0.4 DDD, 0.84 (CI 0.7–1.00); >0.4 DDD, 1.02 (CI 0.84–1.23)
Ueda et al., *JAMA Int Med*, 2024[112]	Adults (almost all with T2D) who initiated GLP-1RA vs. SGLT2i in Denmark and Sweden, nationwide register data 2013–2021	Any GLP-1RA = 124 517 most commonly liraglutide (50%), semaglutide (41%) SGLT2i = 174 036 Mean age 60 years, 45% women, 73% metformin, 22% insulin, no data on BMI	Active-comparator new-user cohort study, PS weighting of confounders Suicide death, self-harm, diagnoses/prescriptions for depression or anxiety as outcomes Adjustment for sociodemography, comorbidity, drugs, markers of healthcare use (not BMI)	Mean follow-up 2.5 years	Incidence rate for suicide death was 0.23 in GLP-1RA vs. 0.18 in SGLT2i per 1000 person-years (HR 1.25; 95% CI 0.83–1.88) Nonfatal self-harm HR 0.77 (95% CI, 0.65–0.91) Depression/anxiety HR 1.01 (95% CI, 0.97–1.06)
Tang et al., *Ann Int Med*, 2024[113]	People aged ≥65 years with T2D who initiated GLP-1 RA vs. SGLT2i and vs. DPP4i, based on 15% sample of national Medicare administrative claims data in the US 2016–2020	Two PS-matched cohorts of patients with T2D: GLP-1RA vs. SGLT2i = 43 614 GLP-1 RA vs. DPP4i = 42 804. Mean age 73 years, 51%–54% women, 36% obesity diagnosis	Population-based cohort study emulating a target trial Suicidal ideation, suicide attempt, and intentional self-harm as outcomes PS-weighting of confounders: demographics, comorbidities, co-medications	Median follow-up 1.6 years	Incidence rate for suicidal ideation and behaviours was 2.4 for GLP-1 RA and 2.2 for SGLT2i users per 1000 person-years (HR 1.07 [95% CI 0.80–1.45]). Compared with DPP4i, HR was 0.94 (95% CI 0.71–1.24)
Douros et al., *Diabetes Care*, 2018[118]	People with T2D initiating antidiabetic drugs between 2007 and 2015 in the UK, based on the U.K. Clinical Practice Research Datalink (CPRD)	Any GLP-1RA = 444; other oral antidiabetics = 10 431 Mean age GLP-1RA 63 vs. 57 years, 45% vs. 39% women, BMI ≥ 30 in 93% vs. 54%	Cohort study with Cox regression, time-varying drug exposure comparing use of GLP-1 RAs with current use of two or more oral antidiabetic drugs Incident diabetic retinopathy as outcome Adjustment for comorbidities, comedications, lifestyle behaviours, cardiometabolic factors, BMI	Median follow-up 0.8 years	GLP-1 RA was not associated with risk of incident diabetic retinopathy overall (HR 1.00, 95% CI 0.85–1.17), and GLP-1RA decreased the risk vs. insulin use (HR 0.67, 95% CI 0.51–0.90) Secondary analyses suggested transient 44% increased Retinopathy risk with GLP-1 RA durations ranging 6 and 12 months

TABLE 3 (Continued)

Comparative safety (adverse effects)					
Study	**Study population and data source**	**Number and characteristics of GLP-1RA exposed people**	**Design and methodology**	**Duration of follow-up**	**Main findings**
Zheng et al., *BMC Med*, 2023[115]	Patients with T2D and without retinopathy treated with GLP-1RAs, matched to those treated with metformin or SU, Swedish Diabetes Register, 2006–2015	Two matched cohorts: Any GLP-1RA = 2390 Metformin or SU = 11 729 Average age 53 years	Matched cohort study with Cox regression, Swedish Diabetes Register Incident diabetic retinopathy as outcome Adjustment for demographics, education, cardiometabolic factors	Median follow-up 2.0 years	GLP-1RA associated with reduced aHR for incident diabetic retinopathy of 0.42 (95% CI 0.29–0.61) Mendelian randomization analyses confirmed a gradually decreased risk of retinopathy with increased expression of the GLP-1 RA gene target
Wai et al., *Am J Ophthalmol* 2023[119]	Patients with diabetes and non-proliferative diabetic retinopathy, based on TriNetX electronic records research network in the US, 2003–2023	Two PS-matched cohorts: Any GLP-1RA = 6481 SGLT2i = 6481 Mean age 65 years, 47% female, BMI 32–33, HbA1c 8.5%	PS-matched cohort study Conversion to proliferative diabetic retinopathy and vitrectomy as outcomes Matching on demographics, BMI, HbA1c, diabetes and retinopathy severity	Follow-up up to 3 years	GLP-1RA had higher rates of conversion to PDR relative to the SGLT2i group (5.4% vs. 4.2%, relative risk 1.28 [1.10–1.50] at 3 years), more diabetic macular oedema (24.2% vs. 18.8%, relative risk 1.29 [1.21–1.38]), but similar rates of vitrectomy surgery (0.7% vs. 0.8%, relative risk 0.89 [0.60–1.31])
Simonsen et al., *MedRxiv* 2024[122]	Adults with T2D who initiated semaglutide vs. SGLT2i during 2018–2022 (Norway) and 2018–2024 (Denmark), nationwide register data	SMR-weighted population: Semaglutide = 60 887 SGLT2i = 60 763 Mean age ca. 60 years, 46% women	Active comparator new-user cohort study Non-arteritic anterior ischemic optic neuropathy (NAION) as outcome PS weighing of confounders (demographics, comorbidities, comedications) and supplementary self-controlled analysis	Not given	Incidence rate of NAION per 10 000 person-years: 2.19 for semaglutide and 1.18 for SGLT2i in Denmark, 2.90 for semaglutide vs. 0.92 for SGLT2i in Norway. Pooled aHR of 2.81 (CI 1.67–4.75), and rate difference for NAION of +1.41 (95% CI +0.53 to +2.29) per 10 000 person-years associated with semaglutide
Grauslund, *Int J Retina Vitr*, 2024[121]	All adults with prevalent or incident T2D in Denmark, nationwide registers, 2018–2023	New initiators of semaglutide (Ozempic) = 106 454 Non-exposed = 317 698 Mean age 65 years, 45% women, median HbA1c 50 mmol/mol	Cohort study comparing risk time in semaglutide exposed and unexposed with Cox regression Non-arteritic anterior ischemic optic neuropathy (NAION) as outcome	Not given	Incidence rate of NAION per 10 000 person-years was 2.3 for semaglutide and 0.9 for non-exposed, corresponding to an adjusted HR of 2.19 (95% CI 1.54–3.12) and a rate difference for NAION of +1.41 (95% CI +0.53 to +2.29) per 10 000 person-years associated with semaglutide

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; DDD, defined daily dose; DPP4i, dipeptidyl-peptidase 4 inhibitors; HR, hazard ratio; PS, propensity score; SU, sulfonylurea; T2D, type 2 diabetes.

obesity population and, in particular, long-term safety outcomes remain insufficiently studied. Future research should focus on comparative effectiveness, long-term clinical impacts, treatment discontinuation effects and cost-effectiveness to optimise the real-world application of these therapies. Addressing these gaps will be crucial for refining clinical guidelines, ensuring equitable access and guiding future pharmacological strategies for obesity management.

ACKNOWLEDGEMENT

This article was commissioned by the Editor as part of a Themed issue on Obesity made possible by funding from Novo Nordisk & Eli Lilly & Co. Sponsor identity was not disclosed to the authors prior to publication.

CONFLICT OF INTEREST STATEMENT

Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma(all regulator-mandated phase IV-studies), and an unrestricted research grant from Novo Nordisk, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this article. Reimar W. Thomsen reports that he has given single scientific presentations on medical research (both with and without financial compensation) for companies, including AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi. The Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the current study. Julie B. Løhdes PhD project is financed by the Novo Nordisk Foundation. Aurelie Mailhac reports no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16364.

DATA AVAILABILITY STATEMENT

This narrative review includes no original research data to be shared; almost all included papers can be found at PubMed.

ORCID

Reimar W. Thomsen https://orcid.org/0000-0001-9135-3474
Anton Pottegård https://orcid.org/0000-0001-9314-5679

REFERENCES

1. Lingvay I, Cohen RV, Roux CWL, Sumithran P. Obesity in adults. *Lancet*. 2024;404(10456):972-987.
2. Gilden AH, Catenacci VA, Taormina JM. Obesity. *Ann Intern Med*. 2024;177(5):Itc65-itc80.
3. Ng M, Dai X, Cogen RM, et al. National-level and state-level prevalence of overweight and obesity among children, adolescents, and adults in the USA, 1990-2021, and forecasts up to 2050. *Lancet*. 2024;404(10469):2278-2298.
4. World Health Organization. *Obesity and overweight 2024*. 2024. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
5. Gribsholt SB, Farkas DK, Thomsen RW, Richelsen B, Sørensen HT. Mortality among Danish patients with a hospital diagnosis of overweight or obesity over a 40-year period. *Clin Epidemiol*. 2022;14:309-325.
6. Valenzuela PL, Carrera-Bastos P, Castillo-García A, Lieberman DE, Santos-Lozano A, Lucia A. Obesity and the risk of cardiometabolic diseases. *Nat Rev Cardiol*. 2023;20(7):475-494.
7. Bray GA, Ryan DH. Evidence-based weight loss interventions: individualized treatment options to maximize patient outcomes. *Diabetes Obes Metab*. 2021;23(Suppl 1):50-62.
8. Yanovski SZ, Yanovski JA. Approach to obesity treatment in primary care: a review. *JAMA Intern Med*. 2024;184(7):818-829.
9. Cornier MA. A review of current guidelines for the treatment of obesity. *Am J Manag Care*. 2022;28(15 Suppl):S288-S296.
10. Müller TD, Blüher M, Tschöp MH, DiMarchi RD. Anti-obesity drug discovery: advances and challenges. *Nat Rev Drug Discov*. 2022;21(3):201-223.
11. Holst JJ. GLP-1 physiology in obesity and development of incretin-based drugs for chronic weight management. *Nat Metab*. 2024;6(10):1866-1885.
12. Iannone A, Natale P, Palmer SC, et al. Clinical outcomes associated with drugs for obesity and overweight: a systematic review and network meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2023;25(9):2535-2544.
13. Andreasen CR, Andersen A, Vilsbøll T. The future of incretins in the treatment of obesity and non-alcoholic fatty liver disease. *Diabetologia*. 2023;66(10):1846-1858.
14. Alfaris N, Waldrop S, Johnson V, Boaventura B, Kendrick K, Stanford FC. GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity: a narrative review. *EClinicalMedicine*. 2024;75:102782.
15. Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet*. 2024;403(10434):e21-e31.
16. Mailhac A, Pedersen L, Pottegård A, et al. Semaglutide (Ozempic(®)) use in Denmark 2018 through 2023 – user trends and off-label prescribing for weight loss. *Clin Epidemiol*. 2024;16:307-318.
17. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373(1):11-22.
18. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002.
19. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205-216.
20. Ahmad NN, Robinson S, Kennedy-Martin T, Poon JL, Kan H. Clinical outcomes associated with anti-obesity medications in real-world practice: a systematic literature review. *Obes Rev*. 2021;22(11):e13326.
21. Henderson K, Sloan CE, Bessesen DH, Arterburn D. Effectiveness and safety of drugs for obesity. *BMJ*. 2024;384:e072686.
22. Suissa K, Schneeweiss S, Kim DW, Patorno E. Prescribing trends and clinical characteristics of patients starting antiobesity drugs in the United States. *Diabetes Obes Metab*. 2021;23(7):1542-1551.
23. Elangovan A, Shah R, Smith ZL. Pharmacotherapy for obesity-trends using a population level national database. *Obes Surg*. 2021;31(3):1105-1112.

24. Ruiz PL, Karlstad Ø, Nøkleby K, et al. Pharmacological treatment of obesity in adults in Norway 2004-2022. *Diabetes Obes Metab*. 2024;26(6):2102-2110.
25. Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med*. 2022;28(10):2083-2091.
26. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221-2232.
27. Yao H, Zhang A, Li D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. *BMJ*. 2024;384:e076410.
28. Karagiannis T, Bekiari E, Tsapas A. Socioeconomic aspects of incretin-based therapy. *Diabetologia*. 2023;66(10):1859-1868.
29. Palanca A, Ampudia-Blasco FJ, Calderón JM, et al. Real-world evaluation of GLP-1 receptor agonist therapy persistence, adherence and therapeutic inertia among obese adults with type 2 diabetes. *Diabetes Ther*. 2023;14(4):723-736.
30. Lassen MCH, Johansen ND, Modin D, et al. Adherence to glucagon-like peptide-1 receptor agonist treatment in type 2 diabetes mellitus: a nationwide registry study. *Diabetes Obes Metab*. 2024;26(11):5239-5250.
31. Kassem S, Khalaila B, Stein N, Saliba W, Zaina A. Efficacy, adherence and persistence of various glucagon-like peptide-1 agonists: nationwide real-life data. *Diabetes Obes Metab*. 2024;26(10):4646-4652.
32. Weiss T, Carr RD, Pal S, et al. Real-world adherence and discontinuation of glucagon-like peptide-1 receptor agonists therapy in type 2 diabetes mellitus patients in the United States. *Patient Prefer Adherence*. 2020;14:2337-2345.
33. Do D, Lee T, Peasah SK, Good CB, Inneh A, Patel U. GLP-1 receptor agonist discontinuation among patients with obesity and/or type 2 diabetes. *JAMA Netw Open*. 2024;7(5):e2413172.
34. Rodriguez PJ, Zhang V, Gratzl S, et al. Discontinuation and reinitiation of dual-labeled GLP-1 receptor agonists among US adults with overweight or obesity. *JAMA Netw Open*. 2025;8(1):e2457349.
35. Gleason PP, Urick BY, Marshall LZ, Friedlander N, Qiu Y, Leslie RS. Real-world persistence and adherence to glucagon-like peptide-1 receptor agonists among obese commercially insured adults without diabetes. *J Manag Care Spec Pharm*. 2024;30(8):860-867.
36. Gasoyan H, Pfoh ER, Schulte R, Le P, Rothberg MB. Early- and later-stage persistence with antiobesity medications: a retrospective cohort study. *Obesity (Silver Spring)*. 2024;32(3):486-493.
37. Ladebo L, Ernst MT, Mailhac A, Dirksen C, Bojsen-Møller KN, Pottegård A. Real-world use of semaglutide for weight management: patient characteristics and dose titration-a Danish cohort study. *Diabetes Care*. 2024;47(10):1834-1837.
38. Mailhac A, Pedersen L, Petersen I, Pottegård A, Sørensen H, Reimar T. *Discontinuation of semaglutide (Wegovy®) therapy for weight loss: population-based study of the first 89,302 users in Denmark (Unpublished manuscript)*. 2025.
39. Mayor S. Socioeconomic disadvantage is linked to obesity across generations, UK study finds. *BMJ*. 2017;356:j163.
40. Hjort MF, Astrup A. Social inequity in health among patients with severe obesity and multimorbidity. *Dan Med J*. 2024;71(7):A01240059. doi:10.61409/A01240059
41. Celletti F, Branca F, Farrar J. Obesity and glucagon-like peptide-1 receptor agonists. *JAMA*. 2025;333(7):561-562.
42. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63(25 Pt B):2985-3023.
43. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22-(Suppl 3):1-203.
44. Yurista SR, Eder RA, Feeley M, Kodur N, Tang WHW, Nguyen CT. A closer look at ACC/AHA and ESC guidelines for managing obesity and overweight in adults. *JACC Adv*. 2023;2(7):100570.
45. Gaskin CJ, Cooper K, Stephens LD, Peeters A, Salmon J, Porter J. Clinical practice guidelines for the management of overweight and obesity published internationally: a scoping review. *Obes Rev*. 2024;25(5):e13700.
46. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;74(10):1376-1414.
47. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227-3337.
48. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ*. 2020;192(31):E875-E891. doi:10.1503/cmaj.191707
49. Grunvald E, Shah R, Hernaez R, et al. AGA clinical practice guideline on pharmacological interventions for adults with obesity. *Gastroenterology*. 2022;163(5):1198-1225.
50. Ard JD, Hong YR, Foster GD, Medcalf A, Nadolsky S, Cardel MI. Twelve-month analysis of real-world evidence from a telehealth obesity-treatment provider using antiobesity medications. *Obesity (Silver Spring)*. 2024;32(12):2246-2254.
51. Mayer CS, Fontelo P. Semaglutide use in people with obesity and type 2 diabetes from real-world utilization data: an analysis of the all of US program. *Diabetes Obes Metab*. 2024;26(11):4989-4995.
52. Gasoyan H, Pfoh ER, Schulte R, Le P, Butsch WS, Rothberg MB. One-year weight reduction with semaglutide or liraglutide in clinical practice. *JAMA Netw Open*. 2024;7(9):e2433326.
53. Talay L, Vickers M. Effectiveness and care continuity in an app-based, glucagon-like peptide-1 receptor agonist-supported weight-loss service for women with overweight and obesity in the UK: a real-world retrospective cohort analysis. *Diabetes Obes Metab*. 2024;26(7):2984-2987.
54. Talay L, Alvi O. Digital healthcare solutions to better achieve the weight loss outcomes expected by payors and patients. *Diabetes Obes Metab*. 2024;26(6):2521-2523.
55. Oral A, Küçük C, Köse M. Real-world clinical effectiveness of liraglutide for weight management in Türkiye: insights from the LIRA-TR study. *J Clin Med*. 2024;13(20):6121.
56. Alabduljabbar K, Alsaqaaby M, Neff KJ, Crotty M, le Roux CW. Weight loss response in patients with obesity treated with injectable semaglutide in a real-world setting. *Endocrine*. 2024;83(2):392-398.
57. Ruseva A, Michalak W, Zhao Z, Fabricatore A, Hartaigh B, Umashanker D. Semaglutide 2.4 mg clinical outcomes in patients with obesity or overweight in a real-world setting: a 6-month retrospective study in the United States (SCOPE). *Obes Sci Pract*. 2024;10(1):e737.
58. Ghusn W, Fansa S, Anazco D, et al. Weight loss and cardiovascular disease risk outcomes of semaglutide: a one-year multicentered study. *Int J Obes (Lond)*. 2024;48(5):662-667.
59. Buckley A, Suliman S, Allum M, et al. Real world use of tirzepatide in the treatment of type 2 diabetes in an Arab population. *Diabetes Obes Metab*. 2024;26(8):3381-3391.
60. Kelly MS, Scopelliti EM, Goodson KE, Lo CMA, Nguyen HX, Simon B. Real-world evaluation of the effects of tirzepatide in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2024;26(12):5661-5668.
61. Alsheikh A, Alshehri A, Alzahrani S, et al. Evaluating the clinical effectiveness and safety of semaglutide in individuals with

uncontrolled type 2 diabetes. Real-world evidence from Saudi Arabia: the observational, multicenter, 15-month EVOLUTION study. *Diabetes Ther*. 2024;15(2):473-485.
62. Caballero Mateos I, García de Lucas MD, Doulatram-Gamgaram VK, et al. Real-world evaluation of once-weekly subcutaneous semaglutide in patients with type 2 diabetes mellitus in Spain (SEMA-RW study). *Nutrients*. 2024;16(15):2545.
63. Rudofsky G, Menzen M, Potier L, et al. Glucagon-like peptide-1 receptor agonist-experienced adults with type 2 diabetes switching to once-weekly semaglutide in a real-world setting: SURE program post hoc analysis. *Adv Ther*. 2024;42(2):788-800. doi:10.1007/s12325-024-03000-x
64. Butt MD, Ong SC, Rafiq A, et al. Long-term clinical efficacy of liraglutide for type 2 diabetes: real-world evidence and outcomes from Pakistan. *J Pharm Policy Pract*. 2024;17(1):2432462.
65. Powell W, Song X, Mohamed Y, et al. Medications and conditions associated with weight loss in patients prescribed semaglutide based on real-world data. *Obesity (Silver Spring)*. 2023;31(10):2482-2492. doi:10.1002/oby.23859
66. Yale JF, Bodholdt U, Catarig AM, et al. Real-world use of once-weekly semaglutide in patients with type 2 diabetes: pooled analysis of data from four SURE studies by baseline characteristic subgroups. *BMJ Open Diabetes Res Care*. 2022;10(2):e002619.
67. Ghusn W, De la Rosa A, Sacoto D, et al. Weight loss outcomes associated with semaglutide treatment for patients with overweight or obesity. *JAMA Netw Open*. 2022;5(9):e2231982.
68. Park JH, Kim JY, Choi JH, et al. Effectiveness of liraglutide 3 mg for the treatment of obesity in a real-world setting without intensive lifestyle intervention. *Int J Obes (Lond)*. 2021;45(4):776-786.
69. Lingvay I, Kirk AR, Lophaven S, Wolden ML, Shubrook JH. Outcomes in GLP-1 RA-experienced patients switching to once-weekly semaglutide in a real-world setting: the retrospective, observational EXPERT study. *Diabetes Ther*. 2021;12(3):879-896.
70. Brown RE, Bech PG, Aronson R. Semaglutide once weekly in people with type 2 diabetes: real-world analysis of the Canadian LMC diabetes registry (SPARE study). *Diabetes Obes Metab*. 2020;22(11):2013-2020.
71. Suliman M, Buckley A, Al Tikriti A, et al. Routine clinical use of liraglutide 3 mg for the treatment of obesity: outcomes in non-surgical and bariatric surgery patients. *Diabetes Obes Metab*. 2019;21(6):1498-1501.
72. Mata-Cases M, Franch-Nadal J, Ortega E, et al. Glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: real-world evidence from a Mediterranean area. *Curr Med Res Opin*. 2019;35(10):1735-1744.
73. Lapolla A, Berra C, Boemi M, et al. Long-term effectiveness of liraglutide for treatment of type 2 diabetes in a real-life setting: a 24-month, multicenter, non-interventional, retrospective study. *Adv Ther*. 2018;35(2):243-253. doi:10.1007/s12325-017-0652-2
74. Moiz A, Filion KB, Toutounchi H, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists for weight loss among adults without diabetes: a systematic review of randomized controlled trials. *Ann Intern Med*. 2025;178(2):199-217. doi:10.7326/ANNALS-24-01590
75. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10278):971-984.
76. Chang KC, Shao SC, Kuo S, et al. Comparative effectiveness of dulaglutide versus liraglutide in Asian type 2 diabetes patients: a multi-institutional cohort study and meta-analysis. *Cardiovasc Diabetol*. 2020;19(1):172.
77. Morieri ML, Rigato M, Frison V, et al. Effectiveness of dulaglutide vs liraglutide and exenatide once-weekly. A real-world study and meta-analysis of observational studies. *Metabolism*. 2020;106:154190.
78. Giorgino F, Guerci B, Füchtenbusch M, et al. The real-world observational prospective study of health outcomes with dulaglutide and liraglutide in patients with type 2 diabetes (TROPHIES): final, 24-month analysis of time to first significant treatment change, treatment persistence and clinical outcomes. *Diabetes Obes Metab*. 2023;25(12):3465-3477.
79. Rodriguez PJ, Goodwin Cartwright BM, Gratzl S, et al. Semaglutide vs tirzepatide for weight loss in adults with overweight or obesity. *JAMA Intern Med*. 2024;184(9):1056-1064.
80. Chuang MH, Chen JY, Wang HY, Jiang ZH, Wu VC. Clinical outcomes of tirzepatide or GLP-1 receptor agonists in individuals with type 2 diabetes. *JAMA Netw Open*. 2024;7(8):e2427258.
81. Anson M, Henney AE, Broadwell N, et al. Incidence of new onset type 2 diabetes in adults living with obesity treated with tirzepatide or semaglutide: real world evidence from an international retrospective cohort study. *EClinicalMedicine*. 2024;75:102777.
82. Huang YN, Liao WL, Huang JY, et al. Long-term safety and efficacy of glucagon-like peptide-1 receptor agonists in individuals with obesity and without type 2 diabetes: a global retrospective cohort study. *Diabetes Obes Metab*. 2024;26(11):5222-5232.
83. Gudzune KA, Kushner RF. Medications for obesity: a review. *JAMA*. 2024;332(7):571-584.
84. Camilleri M, Lupianez-Merly C. Effects of GLP-1 and other gut hormone receptors on the gastrointestinal tract and implications in clinical practice. *Am J Gastroenterol*. 2024;119(6):1028-1037.
85. Shu Y, He X, Wu P, Liu Y, Ding Y, Zhang Q. Gastrointestinal adverse events associated with semaglutide: a pharmacovigilance study based on FDA adverse event reporting system. *Front Public Health*. 2022;10:996179.
86. Karagiannis T, Avgerinos I, Liakos A, et al. Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis. *Diabetologia*. 2022;65(8):1251-1261.
87. Karagiannis T, Malandris K, Avgerinos I, et al. Subcutaneously administered tirzepatide vs semaglutide for adults with type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. *Diabetologia*. 2024;67(7):1206-1222.
88. Sørensen MS, Pottegård A, Andersen NE, Thomsen RW, Lundby C. Survey among adult users of semaglutide for weight loss in Denmark: user characteristics, treatment expectations and experienced effects. *Diabetes Obes Metab*. 2025;27:2214-2222. doi:10.1111/dom.16222
89. Gorgojo-Martínez JJ, Mezquita-Raya P, Carretero-Gómez J, et al. Clinical recommendations to manage gastrointestinal adverse events in patients treated with Glp-1 receptor agonists: a multidisciplinary expert consensus. *J Clin Med*. 2022;12(1):145. doi:10.3390/jcm12010145
90. Gudin B, Ladhari C, Robin P, et al. Incretin-based drugs and intestinal obstruction: a pharmacovigilance study. *Therapie*. 2020;75(6):641-647.
91. Sodhi M, Rezaeianzadeh R, Kezouh A, Etminan M. Risk of gastrointestinal adverse events associated with glucagon-like peptide-1 receptor agonists for weight loss. *JAMA*. 2023;330(18):1795-1797.
92. Suissa K, Cromer SJ, Patorno E. GLP-1 receptor agonists and gastrointestinal adverse events. *JAMA*. 2024;331(10):884-885.
93. American Society of Anesthesiologists. *Patients Taking Popular Medications for Diabetes and Weight Loss Should Stop Before Elective Surgery, ASA Suggests*. 2023. https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/patients-taking-popular-medications-for-diabetes-and-weight-loss-should-stop-before-elective-surgery
94. He L, Wang J, Ping F, et al. Association of glucagon-like peptide-1 receptor agonist use with risk of gallbladder and biliary diseases: a

systematic review and meta-analysis of randomized clinical trials. *JAMA Intern Med*. 2022;182(5):513-519.
95. Yang W, Wu H, Cai X, et al. Weight reduction and the risk of gallbladder and biliary disease: a systematic review and meta-analysis of randomized clinical trials. *Obes Rev*. 2024;25(6):e13725.
96. Zeng Q, Xu J, Mu X, Shi Y, Fan H, Li S. Safety issues of tirzepatide (pancreatitis and gallbladder or biliary disease) in type 2 diabetes and obesity: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2023;14:1214334.
97. Abd El Aziz M, Cahyadi O, Meier JJ, Schmidt WE, Nauck MA. Incretin-based glucose-lowering medications and the risk of acute pancreatitis and malignancies: a meta-analysis based on cardiovascular outcomes trials. *Diabetes Obes Metab*. 2020;22(4):699-704.
98. Nreu B, Dicembrini I, Tinti F, Mannucci E, Monami M. Pancreatitis and pancreatic cancer in patients with type 2 diabetes treated with glucagon-like peptide-1 receptor agonists: an updated meta-analysis of randomized controlled trials. *Minerva Endocrinol (Torino)*. 2023;48(2):206-213.
99. Thomsen RW, Pedersen L, Møller N, Kahlert J, Beck-Nielsen H, Sørensen HT. Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case-control study. *Diabetes Care*. 2015;38(6):1089-1098.
100. Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. *BMJ*. 2014;348:g2366.
101. Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-like peptide 1 receptor agonists and 13 obesity-associated cancers in patients with type 2 diabetes. *JAMA Netw Open*. 2024;7(7):e2421305.
102. Dankner R, Murad H, Agay N, Olmer L, Freedman LS. Glucagon-like peptide-1 receptor agonists and pancreatic cancer risk in patients with type 2 diabetes. *JAMA Netw Open*. 2024;7(1):e2350408.
103. Masson W, Lobo M, Barbagelata L, Lavalle-Cobo A, Nogueira JP. Acute pancreatitis due to different semaglutide regimens: an updated meta-analysis. *Endocrinol Diabetes Nutr (Engl Ed)*. 2024;71(3):124-132.
104. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology*. 2010;151(4):1473-1486.
105. Hu W, Song R, Cheng R, et al. Use of GLP-1 receptor agonists and occurrence of thyroid disorders: a meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2022;13:927859.
106. Pasternak B, Wintzell V, Hviid A, et al. Glucagon-like peptide 1 receptor agonist use and risk of thyroid cancer: Scandinavian cohort study. *BMJ*. 2024;385:e078225.
107. Baxter SM, Lund LC, Andersen JH, et al. Glucagon-like peptide 1 receptor agonists and risk of thyroid cancer: an international multisite cohort study. *Thyroid*. 2025;35(1):69-78.
108. Rohde C, Schmitz N, Thomsen RW, Østergaard SD. Incident psychopharmacological treatment and psychiatric hospital contact in individuals with newly developed type 2 diabetes - a register-based cohort study. *Acta Neuropsychiatr*. 2021;33(2):72-84.
109. Cooper DH, Ramachandra R, Ceban F, et al. Glucagon-like peptide 1 (GLP-1) receptor agonists as a protective factor for incident depression in patients with diabetes mellitus: a systematic review. *J Psychiatr Res*. 2023;164:80-89.
110. Gribsholt SB, Thomsen RW, Farkas DK, Sørensen HT, Richelsen B, Svensson E. Changes in prescription drug use after gastric bypass surgery: a nationwide cohort study. *Ann Surg*. 2017;265(4):757-765.
111. Castaneda D, Popov VB, Wander P, Thompson CC. Risk of suicide and self-harm is increased after bariatric surgery-a systematic review and meta-analysis. *Obes Surg*. 2019;29(1):322-333.
112. Ueda P, Söderling J, Wintzell V, et al. GLP-1 receptor agonist use and risk of suicide death. *JAMA Intern Med*. 2024;184(11):1301-1312.
113. Tang H, Lu Y, Donahoo WT, et al. Glucagon-like peptide-1 receptor agonists and risk for suicidal ideation and behaviors in U.S. older adults with type 2 diabetes: a target trial emulation study. *Ann Intern Med*. 2024;177(8):1004-1015.
114. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
115. Zheng D, Li N, Hou R, et al. Glucagon-like peptide-1 receptor agonists and diabetic retinopathy: nationwide cohort and Mendelian randomization studies. *BMC Med*. 2023;21(1):40.
116. Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA(1c) change and diabetic retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: a meta-analysis and meta-regression. *Diabetes Care*. 2021;44(1):290-296.
117. Vilsbøll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes Obes Metab*. 2018;20(4):889-897.
118. Douros A, Filion KB, Yin H, et al. Glucagon-like peptide 1 receptor agonists and the risk of incident diabetic retinopathy. *Diabetes Care*. 2018;41(11):2330-2338.
119. Wai KM, Mishra K, Koo E, et al. Impact of GLP-1 agonists and SGLT-2 inhibitors on diabetic retinopathy progression: an aggregated electronic health record data study. *Am J Ophthalmol*. 2024;265:39-47.
120. Hathaway JT, Shah MP, Hathaway DB, et al. Risk of nonarteritic anterior ischemic optic neuropathy in patients prescribed semaglutide. *JAMA Ophthalmol*. 2024;142(8):732-739. doi:10.1001/jamaophthalmol.2024.2296
121. Grauslund J, Taha AA, Molander LD, et al. Once-weekly semaglutide doubles the five-year risk of nonarteritic anterior ischemic optic neuropathy in a Danish cohort of 424,152 persons with type 2 diabetes. *Int J Retina Vitreous*. 2024;10(1):97.
122. Simonsen E, Lund L, Ernst M, et al. Use of semaglutide and risk of non-arteritic anterior ischemic optic neuropathy: a Danish-Norwegian cohort study. *Diabetes Obes Metab*. 2025. doi:10.1111/dom.16316
123. Abasheva D, Ortiz A, Fernandez-Fernandez B. GLP-1 receptor agonists in patients with chronic kidney disease and either overweight or obesity. *Clin Kidney J*. 2024;17(Suppl 2):19-35.
124. Sawami K, Tanaka A, Node K. Updated evidence on cardiovascular and renal effects of GLP-1 receptor agonists and combination therapy with SGLT2 inhibitors and finerenone: a narrative review and perspectives. *Cardiovasc Diabetol*. 2024;23(1):410.
125. Westermeier F, Fisman EZ. Glucagon like peptide-1 (GLP-1) agonists and cardiometabolic protection: historical development and future challenges. *Cardiovasc Diabetol*. 2025;24(1):44.
126. Hansen MK, Olesen KKW, Gyldenkerne C, et al. Eligibility for and preventive potential of semaglutide in overweight and obese patients with myocardial infarction. *J Am Coll Cardiol*. 2024;83(9):956-958.
127. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab*. 2022;24(8):1553-1564.
128. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA*. 2021;325(14):1414-1425.
129. Aronne LJ, Sattar N, Horn DB, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA*. 2024;331(1):38-48.

130. Jensen SBK, Blond MB, Sandsdal RM, et al. Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomised placebo-controlled trial. *EClinicalMedicine*. 2024;69:102475. doi:10.1016/j.eclinm.2024.102475
131. Zushin PH, Wu JC. Evaluating the benefits of the early use of GLP-1 receptor agonists. *Lancet*. 2025;405(10474):181-183.
132. Gamble JM, Chibrikov E, Midodzi WK, Twells LK, Majumdar SR. Examining the risk of depression or self-harm associated with incretin-based therapies used to manage hyperglycaemia in patients with type 2 diabetes: a cohort study using the UK clinical practice research datalink. *BMJ Open*. 2018;8(10):e023830.
133. Tsai WH, Sung FC, Chiu LT, Shih YH, Tsai MC, Wu SI. Decreased risk of anxiety in diabetic patients receiving glucagon-like peptide-1 receptor agonist: a Nationwide, population-based cohort study. *Front Pharmacol*. 2022;13:765446.
134. Kessing LV, Rytgaard HC, Ekstrøm CT, Knop FK, Berk M, Gerds TA. Antidiabetes agents and incident depression: a nationwide population-based study. *Diabetes Care*. 2020;43(12):3050-3060.
135. Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Diabetes, antidiabetic medications and risk of depression – a population-based cohort and nested case-control study. *Psychoneuroendocrinology*. 2022;140:105715.
136. Brandkvist M, Bjørngaard JH, Ødegård RA, et al. Genetic associations with temporal shifts in obesity and severe obesity during the obesity epidemic in Norway: a longitudinal population-based cohort (the HUNT study). *PLoS Med*. 2020;17(12):e1003452.
137. Tolstrup JS, Bramming M, Davidsen M, Schramm S. Time trends in body mass index distribution in the general population in Denmark from 1987 to 2021. *Dan Med J*. 2023;70(10):A03230139.
138. Sørensen HT, Christensen T, Bøtker HE, et al. Cohort profile: better health in late life. *Clin Epidemiol*. 2023;15:1227-1239.

How to cite this article: Thomsen RW, Mailhac A, Løhde JB, Pottegård A. Real-world evidence on the utilization, clinical and comparative effectiveness, and adverse effects of newer GLP-1RA-based weight-loss therapies. *Diabetes Obes Metab*. 2025;27(Suppl. 2):66-88. doi:10.1111/dom.16364