Weight Loss Effectiveness of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) When Used with and without Lifestyle Modifications: A Retrospective Real-World Study

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Background

- Combining GLP-1RAs with exercise has been shown to produce greater weight loss than GLP-1RAs alone.[1,2] Diet is also recommended, but its independent effect is less clear.[3]
- This evidence comes largely from randomized controlled trials; real-world studies are few, as lifestyle behaviors are mostly documented in unstructured clinical notes.[2]
- Direct comparisons of lifestyle behaviors (e.g., diet vs. exercise) are also scarce.

Objective

- To assess the role of different lifestyle factors (diet and exercise) on the effectiveness of GLP-1RAs in weight loss using real-world data (RWD).

Methods

Cohort

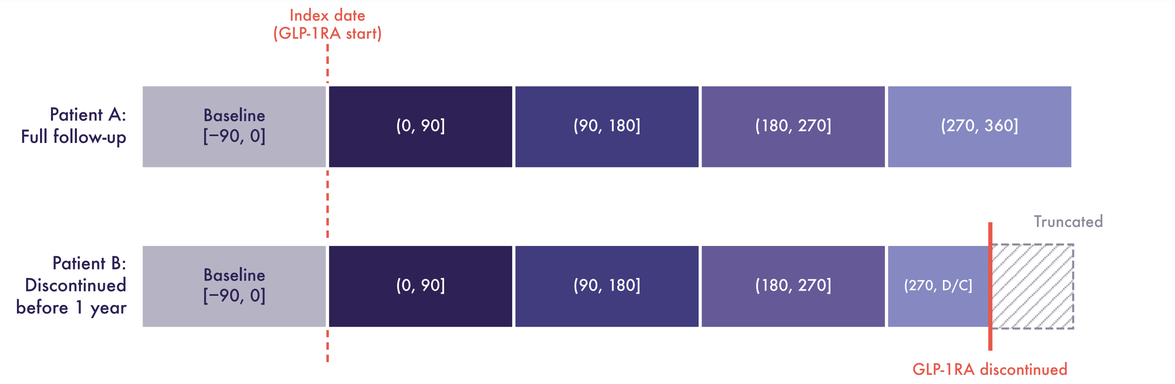
- Patients initiating a GLP-1RA between 2019/01/01 and 2025/07/17 (earliest start or written date = index) were identified using the Veradigm Network EHR.
- A random sample of 24,881 patients was selected for the curation of a GLP-1RA data asset, including lifestyle factors. See **Figure 1** for additional selection criteria.

Figure 1: Patient Selection

Initiated a GLP-1RA between 2019/01/01 and 2025/07/17 (N = 396,916)
↓
Randomly sampled for GLP-1 data curation (N = 24,881)
↓
No history of bariatric surgery (N = 24,546)
↓
Weight and lifestyle data at baseline (N = 5,141)
↓
Weight and lifestyle data in ≥1 post-index window (**N = 2,745**)

Methods (cont'd)

Figure 2: Study Time Windows



Ninety-day windows were created relative to the index date: a baseline window and up to four post-index windows. Follow-up for patients who discontinued their GLP-1RA within the first year was truncated at the discontinuation date.

Variables

- Weight (from structured EHR fields) was averaged within each window (**Figure 2**).
- Diet and exercise engagement were extracted from clinical notes using a large language model-based AI pipeline that was validated by clinicians (>90% accuracy).
- Patients were categorized as no diet/exercise, exercise-only, diet-only, or diet and exercise based on ≥1 positive patient-reported mention of each behavior per window.
- Baseline covariates (from structured EHR fields): type 2 diabetes, obesity (diagnosis or baseline BMI ≥ 30), age, GLP-1RA type, gender, race, and ethnicity.

Analysis

- Weight was modeled via a linear mixed effects model (random patient intercept) and included a time × lifestyle interaction and baseline covariates.
- Differences in weight change per window between all pairs of lifestyle groups were estimated from the model coefficients and Bonferroni-adjusted.

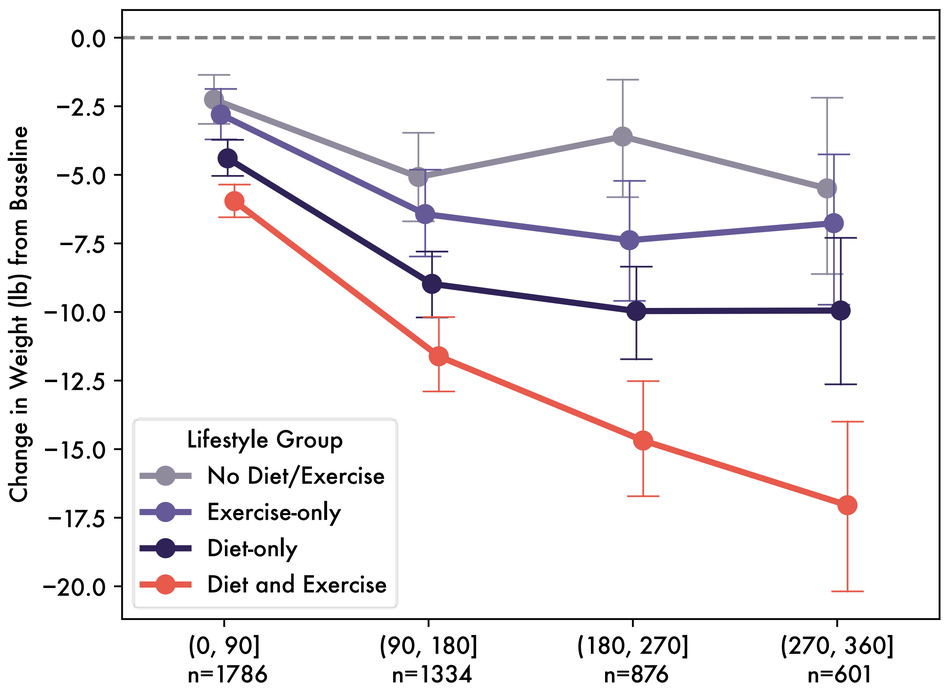
Results

- The study cohort was 64% female, with a mean age of 54 years and mean weight of 221 lb at baseline. Most patients initiated semaglutide (58%) (**Table 1**).
- Adjusted baseline weight did not differ significantly across lifestyle groups (all $p > 0.05$).
- All lifestyle groups had significantly greater weight loss compared to the no diet/exercise group (**Table 2** for adjusted estimates; **Figure 3** for unadjusted trends).
  - Patients who neither dieted nor exercised lost an estimated 1.85 lb per window.
  - Compared to this group, patients lost an additional 2.28 lb (beyond the 1.85 lb) with diet and exercise, 1.25 lb with diet-only, and 0.84 lb with exercise-only.
- Diet and exercise combined was associated with significantly greater weight loss compared to diet-only and exercise-only. Diet-only and exercise-only, however, did not differ significantly ($p = 0.64$).

Table 1: Baseline Patient Characteristics (N = 2,745)

Demographics		Clinical Characteristics	
Age, Mean (SD)	54.1 (13.7)	**Type 2 Diabetes, N (%)**	997 (36.3%)
Female, N (%)	1,765 (64.3%)	**Obesity, N (%)**	2,311 (84.2%)
Race, N (%)		**GLP-1RA Type, N (%)**	
White	1,219 (44.4%)	semaglutide	1,601 (58.3%)
Black	275 (10.0%)	dulaglutide	454 (16.5%)
Asian	95 (3.5%)	tirzepatide	417 (15.2%)
Other	137 (5.0%)	liraglutide	198 (7.2%)
Not Reported	1,019 (37.1%)	lixisenatide	40 (1.5%)
Non-Hispanic, N (%)	2,490 (90.7%)	exenatide	35 (1.3%)
		Weight (lb), Mean (SD)	221.0 (51.7)

Figure 3: Change in Weight from Baseline by Lifestyle Group[a]



[a]Unadjusted mean change in weight (lb) from baseline by lifestyle group. Error bars represent 95% CI.

Table 2: Lifestyle Group Pairwise Comparisons of Weight Change per Window

Group	Compared with	Diff. in Weight (lb) per window (95% CI)[a,b]	p-value[c]
Exercise-only	No Diet/Exercise	-0.84 (-1.43, -0.24)	0.04
Diet-only	Exercise-only	-0.42 (-0.92, 0.09)	0.64
Diet-only	No Diet/Exercise	-1.25 (-1.79, -0.71)	<0.001
Diet and Exercise	Diet-only	-1.03 (-1.48, -0.57)	<0.001
Diet and Exercise	Exercise-only	-1.44 (-1.97, -0.91)	<0.001
Diet and Exercise	No Diet/Exercise	-2.28 (-2.83, -1.72)	<0.001

[a]Differences = Group – Comparison group; Negative values indicate greater weight loss in the Group.
[b]Estimates are adjusted for baseline features described above.
[c]p-values are Bonferroni-adjusted for 6 comparisons.

Conclusions

- GLP-1RA use with lifestyle modifications was associated with greater weight loss than GLP-1RA alone. Diet and exercise combined showed the most weight loss; diet-only and exercise-only did not differ, suggesting complementary effects.
- These real-world findings reinforce the use of GLP-1RAs as an adjunct to diet and exercise.
- AI extraction from clinical notes enabled real-world assessment of lifestyle behaviors not captured in the structured EHR fields.

References

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Disclosures

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