

Gastrointestinal Adverse Effects Following Initiation of Glucagon-Like Peptide-1 Receptor Agonists to Treat Obesity Among Commercially Insured Members Without Diabetes: A 3-Year Real-World Assessment



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Background

- While glucagon-like peptide-1 receptor agonists (GLP-1s) have demonstrated effectiveness in weight reduction in clinical-trial and real-world settings, gastrointestinal (GI) adverse effects (AE) are frequently reported with GLP-1 use.^{1,2}
- Some known GLP-1-associated GI AE like nausea and vomiting are mild and often self-limiting, but severe GI AE—including acute pancreatitis, cholecystitis, and intestinal obstruction—can create substantial healthcare burdens.
- The impact of GLP-1 obesity treatment initiation on the prevalence of severe GI AE in members without diabetes in the real-world setting has not been fully elucidated.

Objective

Our objective was to assess the prevalence of severe GI AE in the year before versus 3 years after GLP-1 obesity treatment initiation among commercially insured members without diabetes compared with matched controls.

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Methods

- This retrospective, observational cohort study analyzed Prime Therapeutics' integrated pharmacy and medical claims data from 16 million commercially insured members from all regions of the United States between January 1, 2020, and March 31, 2025.
- Study inclusion was limited to members newly initiating a GLP-1, as defined as no GLP-1 use in the prior year, between January 1, 2021, and March 31, 2022.
- Inclusion criteria were continuous enrollment in the 12 months prior to index for a new GLP-1 therapy start date (pre-period) and 12 months after index (post-period), an obesity diagnosis on 1 or more medical claims during the pre-period, 19 years of age or older at index, and no GLP-1 use or evidence of diabetes mellitus (DM) during the pre-period.
- Members were excluded if they had a DM diagnosis medical claim, pharmacy DM drug therapy claim, or medical claim diagnosis for HIV/AIDS, hemophilia, sickle cell disease, malignant cancer, or end-stage renal disease during the pre-period.
- Using the same inclusion and exclusion criteria, a control group was identified from a potential pool of 10 million members with at least 1 new pharmacy claim for a maintenance medication between January 1, 2021, and March 31, 2022. Each distinct fill date for a new prescription of a chronic medication was considered a potential index date.
- A 2-step matching approach was used to identify the control group, matching each treatment member to up to 3 control members.
 - Step 1: A direct match was made on gender, 10-year age bands, region, line of business (i.e., fully insured, health insurance marketplace, self-insured), Charlson Comorbidity Index score band,³ pre-period pharmacy claim fill band, quarter and year of index date, hospitalization in the 91-day period before index, prediabetes, severe obesity, sleep apnea, and any weight loss medication use.
 - Step 2: After the direct match, GLP-1 utilizers were matched using propensity scores on age, month of index study date, body mass index (BMI) grouping, Charlson Comorbidity Index score and conditions,³ pre-period pharmacy claim fill rates, pregnancy, and pre-period utilization of non-GLP-1 weight loss drug therapy by class (e.g., phentermine, topiramate, naltrexone), statins, renin-angiotensin system antagonists (RASAs), and/or antidepressants.

- Balance across cohorts was evaluated using standardized mean differences (SMDs), with differences less than 0.1 considered balanced.
- The prevalence of intestinal obstruction, acute pancreatitis, and cholecystectomy were assessed individually and as a single composite outcome in the pre-period and each post-period year.
- All study outcomes were measured as an annual percentage of members with the outcome of interest in the pre-period and each post-period year.
- Annual percentage changes between groups and across periods (pre-period vs. year 1, year 2, and year 3 post-period) were statistically analyzed using difference-in-difference (DID) regression.
 - Quarterly trends were assessed graphically.

Table 1 Select Demographic and Clinical Characteristics After Matching				
	After Matching*			
Demographic or Clinical Characteristic	Treatment (N=7,922)	Control (N=22,998)	SMD†	P Value‡
Age in years, mean (SD)	45.9 (10.1)	45.8 (10.3)	0.006	0.63
Gender–female, N (%)	6,365 (80.3%)	18,504 (80.5%)	0.003	0.84
Charlson Comorbidity Index, mean (SD)	0.26 (0.54)	0.25 (0.52)	0.025	0.06
Severe obesity**, N (%)	3,247 (41.0%)	9,328 (40.6%)	0.009	0.51
BMI Z-code category, N (%)				
30–34.9	1,469 (18.5%)	4,180 (18.2%)	0.042	0.03
35–39.9	1,316 (16.6%)	3,573 (15.5%)		
40–44.9	1,107 (14.0%)	3,400 (14.8%)		
45+	1,054 (13.3%)	2,948 (12.8%)		
No obesity BMI Z-code	2,976 (37.6%)	8,897 (38.7%)		
Index quarter and year, N (%)				
Q1 2021	837 (10.6%)	2,428 (10.6%)	0.003	1.00
Q2 2021	1,271 (16.0%)	3,671 (16.0%)		
Q3 2021	1,542 (19.5%)	4,464 (19.4%)		
Q4 2021	1,814 (22.9%)	5,284 (23.0%)		
Q1 2022	2,458 (31.0%)	7,151 (31.1%)		

standardized mean difference (SMD); standard deviation (SD)
*Eligible control group members were matched to glucagon-like peptide-1 receptor agonist (GLP-1) treatment members on characteristics and conditions using a combined exact and propensity score matching approach, as described in Methods.
**Severe obesity is defined as BMI ≥40 using ICD-10-CM codes of E66.01 or Z68.4. The number of members with severe obesity exceeds the number of members categorized with BMI ≥40 due to coding of E66.01 and under-coding of Z-codes for BMI, which are not billable ICD-10-CM codes.
†SMD assesses the balance of demographics and characteristics between groups, with excellent balance defined as a value <0.1.
‡Statistical comparisons between the treatment and control groups used t-tests for continuous outcomes and chi-square tests for categorical outcomes.

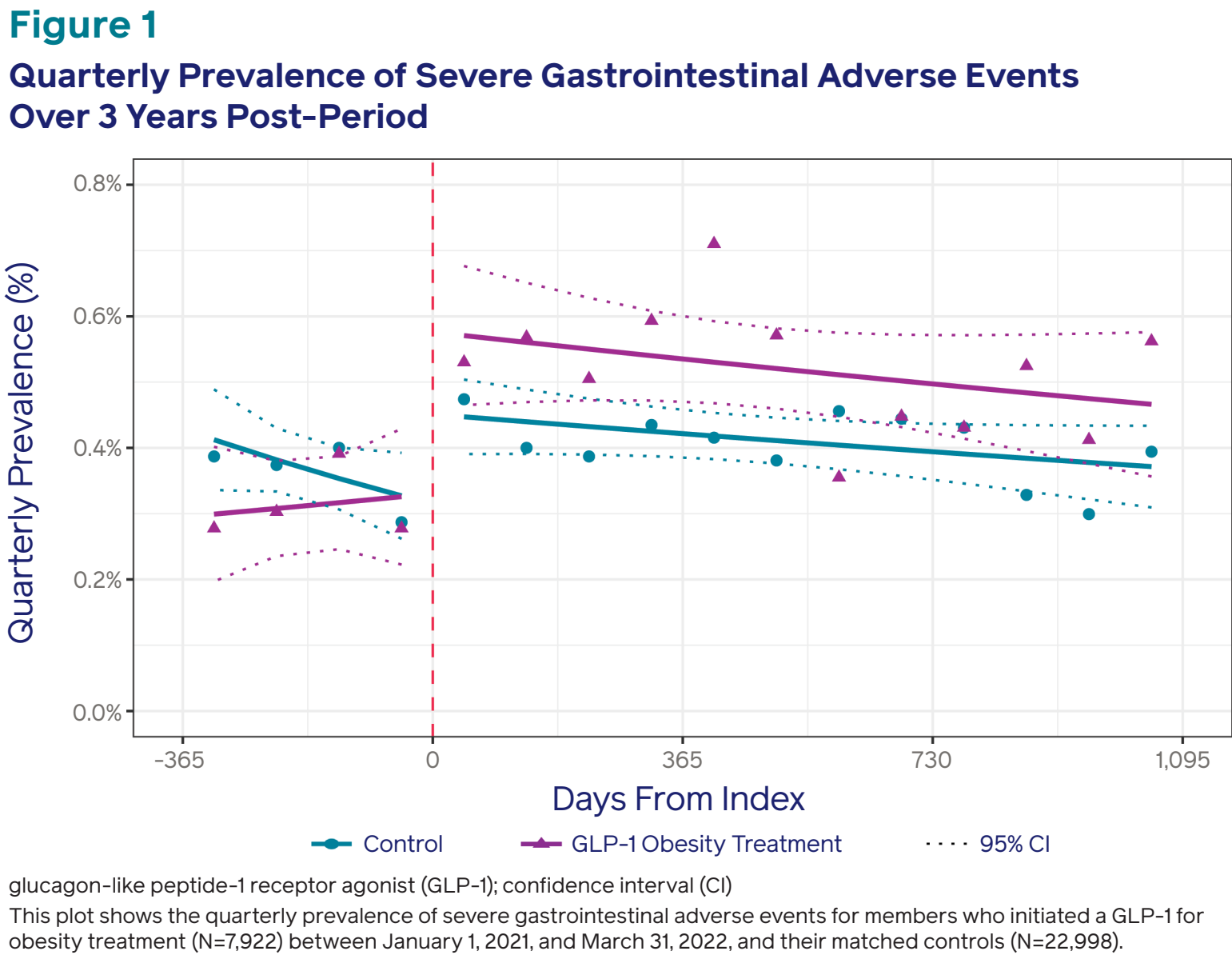


Table 2 Change in Prevalence of Severe Gastrointestinal Adverse Events in Pre-Period vs. Post-Period						
	GLP-1 Obesity Treatment		Matched Controls*		Annual DID vs. Pre-Period** (95% CI)	P Value
	Prevalence (per 1,000 PY)	Difference vs. Pre-Period (% change)	Prevalence (per 1,000 PY)	Difference vs. Pre-Period (% change)		
Pre-period	11.6	—	13.9	—	—	—
Post-period year 1	19.8	8.2 (70.7%)	15.7	1.8 (13.1%)	6.4 (2-10.8)	0.01
Post-period year 2	19.0	7.4 (63.5%)	14.9	1.0 (7.6%)	6.3 (1.6-11.1)	0.01
Post-period year 3	17.1	5.4 (46.8%)	13.0	-0.8 (-5.9%)	6.3 (1.3-11.2)	0.01

glucagon-like peptide-1 receptor agonist (GLP-1); person-years (PY); difference-in-difference (DID); confidence interval (CI)
*Eligible control group members matched to GLP-1 treatment members on characteristics and conditions using a combined exact and propensity score matching approach; see Methods
**Difference between the pre-to-post-period change in prevalence among the GLP-1 cohort and the pre-to-post-period change in prevalence among matched controls

Table 3						
Change in Prevalence of Acute Pancreatitis, Cholecystectomy, and Intestinal Obstruction in Pre-Period vs. Post-Period						
	GLP-1 Obesity Treatment		Matched Controls*		Annual DID vs. Pre-Period** (95% CI)	P Value
	Prevalence (per 1,000 PY)	Difference vs. Pre-Period (% change)	Prevalence (per 1,000 PY)	Difference vs. Pre-Period (% change)		
Acute Pancreatitis						
Pre-period	1.6	—	2.0	—	—	—
Post-period year 1	4.8	3.2 (192.3%)	2.4	0.4 (21.5%)	2.7 (0.8-4.6)	0.01
Post-period year 2	3.1	1.4 (88.1%)	2.3	0.3 (17.3%)	1.1 (-0.7-2.9)	0.23
Post-period year 3	2.6	1 (59.9%)	2.0	0 (1.5%)	1 (-0.9-2.8)	0.32
Cholecystectomy						
Pre-period	7.3	—	8.6	—	—	—
Post-period year 1	11.7	4.4 (60.3%)	9.5	0.9 (10.2%)	3.5 (0-7.1)	0.05
Post-period year 2	11.0	3.6 (49.7%)	8.1	-0.5 (-5.9%)	4.2 (0.5-7.8)	0.03
Post-period year 3	10.5	3.2 (43.3%)	6.4	-2.2 (-25.6%)	5.4 (1.5-9.2)	0.01
Intestinal Obstruction						
Pre-period	3.0	—	3.7	—	—	—
Post-period year 1	5.6	2.5 (83.3%)	4.6	0.8 (22.6%)	1.7 (-0.6-3.9)	0.15
Post-period year 2	5.7	2.7 (88.5%)	5.1	1.3 (36%)	1.3 (-1.3-4)	0.31
Post-period year 3	4.7	1.7 (54.6%)	5.5	1.8 (47.6%)	-0.1 (-2.8-2.5)	0.93

glucagon-like peptide-1 receptor agonist (GLP-1); person-years (PY); difference-in-difference (DID); confidence interval (CI)
*Eligible control group members matched to GLP-1 treatment members on characteristics and conditions using a combined exact and propensity score matching approach; see Methods
**Difference between the pre-to-post-period change in prevalence among the GLP-1 cohort and the pre-to-post-period change in prevalence among matched controls

Results

- Out of the 3,027,817 control member-index date combinations and 8,614 GLP-1 treatment members who met inclusion and exclusion criteria, 22,998 controls were matched to 7,922 treatment members.
- The treatment and control cohorts were well balanced after matching (SMD <0.1; [Table 1](#)).
- For the treatment cohort, prevalence of any severe GI AE increased from 11.6 per 1,000 person-years (PY) in the pre-period to 19.8 per 1,000 PY in post-period year 1 and remained elevated throughout the post-period ([Table 2](#); [Figure 1](#)).
 - For matched controls, prevalence slightly increased in post-period year 1 and fell below pre-period prevalence by post-period year 3.
 - The DID estimates indicated statistically significant higher prevalence in the treatment cohort compared with controls across all 3 post-period years compared with pre-period.
- The number needed to harm occurred at a rate of 1 severe GI event per 156-160 treated members annually.
- Although the highest DID estimates for acute pancreatitis and intestinal obstruction were observed in year 1, the highest estimate for cholecystectomy was found in year 3 ([Table 3](#)).

Limitations

- Data were sourced from administrative healthcare claims; therefore, misclassification bias may have occurred due to the use of medical and pharmacy claims to exclude individuals without diabetes and identify those with obesity. Similarly, claims-based identification of GLP-1 utilization may have failed to appropriately classify utilizers of compounded GLP-1 products, individuals procuring GLP-1 through direct-to-consumer programs, or other individuals with nonadjudicated GLP-1 utilization.
- Observational bias may explain the higher severe GI AE rates seen among GLP-1-treated members as these severe GI AE are well-known GLP-1 therapy risks and, therefore, more diligently screened for by providers.
- Our study examined a commercially insured membership and, therefore, is not generalizable to Medicare or Medicaid populations.
- The impacts of an individual's cost sharing, other diagnoses, social determinants of health, or other member characteristics are outside the scope of this analysis and are worthy of future consideration.

Conclusion

- GLP-1s are known to increase severe GI AE risk; this is the first study to quantify that risk using real-world data. Among commercially insured individuals, there was a statistically significant annual number needed to harm of 1 additional member with a severe GI AE per 160 individuals without diabetes treated with GLP-1s for obesity, compared with matched controls.
- During the first post-period year in this analysis, the GLP-1 treatment group had a significantly higher pancreatitis rate, and cholecystectomy was significantly higher in all 3 years.
- These findings suggest that GLP-1 obesity treatment can increase rates of severe GI AE throughout the first 3 years of treatment, emphasizing the need for early and ongoing cardiometabolic care management.
- Further research into the cost impact of these events is essential to understanding healthcare spending trends following GLP-1 obesity treatment initiation.

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