International Journal of Obesity www.nature.com/ijo

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Epidemiology and Population Health

Weight change from incretin-based weight loss medications across categories of second-generation antipsychotics

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OBJECTIVE: Patients prescribed second-generation antipsychotics (SGA) are at risk of antipsychotic induced weight gain (AIWG). The objective was to estimate weight changes after prescription of incretin-based weight loss medications by category of expected AIWG: high (olanzapine, clozapine), intermediate (risperidone, quetiapine, paliperidone) and low (e.g., asenapine, aripiprazole).
METHODS: We conducted a retrospective cohort study using electronic health records (June 2021–December 2023) from Epic Cosmos for adults (≥18 years) without diabetes, prescribed SGA, and eligible for incretin-based weight loss medications. We studied changes in weight (kg) and the probability of at least 5% weight loss after 6 months of prescription of incretin-based medications by categories of AIWG.
RESULTS: The analytic sample ($n = 66{,}574$) were aged 51.9 years (SD: 17.7), with average BMI of 39.5 kg/m^2 (SD: 7.7). Those prescribed incretin-based medications lost −2.17 kg (95% CI: −2.49, −1.84), and were 1.71 (95% CI: 1.63, 1.80) times more likely to achieve 5% weight loss, relative to those who didn't receive prescriptions. Weight loss was greater among those prescribed SGAs of low AIWG (−3.02 kg, 95% CI: −3.29, −2.74), relative to those prescribed high AIWG (−1.33 kg, 95% CI: −2.04, −0.62).
CONCLUSIONS: Semaglutide and tirzepatide induce weight loss among those prescribed SGAs, with lower effectiveness in those prescribed higher AIWG SGAs.

International Journal of Obesity; https://doi.org/10.1038/s41366-025-01885-4

STUDY IMPORTANCE

What is already known?

- Incretin-based weight loss medications are highly efficacious for weight loss in the general population without diabetes. However, individuals prescribed second generation antipsychotics (SGA) were excluded from published trials.

What does this study add?

- Effectiveness of incretin-based weight loss medications is lower among those prescribed high weight-inducing SGAs, relative to those prescribed low weight-inducing SGAs.

How might these results change the direction of research or the focus of clinical practice?

- These findings may encourage primary care practitioners and psychiatrists to monitor weight changes, especially among those prescribed high weight-inducing SGAs, for promotion of additional weight management strategies.

BACKGROUND

One in 18 adults in the United States have serious mental illnesses like schizophrenia, bipolar disorder, major depression, and schizoaffective disorder [1]. Second generation antipsychotics (SGA) are efficacious in reducing psychiatric symptoms of these illnesses with a lower risk of extrapyramidal symptoms than first generation agents [2]. However, antipsychotic induced weight gain (AIWG) from SGAs, as a consequence of changes in metabolism and appetite regulation, lead to increased cardiovascular risk [3]. Current pharmacological interventions (e.g., metformin, H2 antagonists) for management of AIWG require further evidence before widespread adoption [4].

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Received: 18 April 2025 Revised: 9 July 2025 Accepted: 4 August 2025
Published online: 15 August 2025

Incretin mimetics like Glucagon-like Peptide Receptor Agonists (GLP1-RA) and dual GLP-1 RA/Gastric Inhibitory Peptide were approved for weekly dosage by the US Food and Drug Administration for weight management in June 2021 (semaglutide) and December 2022 (tirzepatide) [5, 6]. To be eligible for semaglutide/tirzepatide, patients needed to have either obesity (body mass index [BMI] ≥30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) and at least one weight related condition (e.g., high blood pressure, hyperlipidemia) [5, 6].

Published phase 3 trials of incretin-based medications for weight loss excluded individuals prescribed SGAs [7]. However, previous studies of liraglutide and exenatide suggest potential benefits among those prescribed SGA without worsening of psychiatric symptoms [8–10]. We hypothesized that incretin mimetics may be helpful in weight management for this vulnerable population. Therefore, our objective was to study whether prescription of semaglutide or tirzepatide was associated with heterogeneity in weight change, by categories of AIWG from SGA, among guideline-based eligible adults with overweight or obesity and without diabetes.

METHODS AND FINDINGS

Study design

We used longitudinal data from the Epic Cosmos Research Platform extracted between June 2021 and December 2023 [11]. This study included data regarding adult patients (18–99 years) from United States without type 1, type 2, or other forms of diabetes who were prescribed a second-generation antipsychotic (Supplementary Table 1) [12]. These patients were also concurrently eligible for incretin-based weight loss medications based on BMI and cardiometabolic comorbidities. We additionally restricted our analysis to those active patients who had at least one inpatient or outpatient encounter in each of the 2 years before prescription of the SGA, and not prescribed other weight loss medications (liraglutide, phentermine, phentermine/topiramate, naltrexone/bupropion, lorcaserin, orlistat) or metformin for weight management in the previous 3 months. Data extraction was conducted between 4 June 2024 and 6 July 2024. Analytic sample selection is presented in Supplementary Fig. 1.

Variables

Exposure. Under an intention-to-treat framework, the exposed group consisted of encounters from patients who were prescribed incretin-based weight loss medications in the calendar month of, or within 2 months, after being prescribed an SGA. We used the 2-month window to reduce immortal time bias between SGA prescription and assessment of weight [13]. The unexposed group consisted of patients who were not prescribed incretin-based weight loss medications. We used nearest neighbor propensity scores, matching each exposed patient to four unexposed patients.

Outcome. The primary outcomes were changes in weight, percentage weight loss, and achievement of 5% weight loss from baseline. We extracted the earliest record of weight (kilograms) in the period between 6 and 9 months following the SGA prescription. A framework for the analysis is provided in Supplementary Fig. 2.

Covariates. Effect modification was assessed after categorizing the index SGA by expected AIWG as high (+++; olanzapine, clozapine), intermediate (++; risperidone, quetiapine, paliperidone) and low (+; aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, ziprasidone) [2].

Age, biological sex, race-ethnicity, and residential location were extracted from the latest available records of each patient. Percentile ranking for the Social Vulnerability Index 2020 data and the Rural-Urban Commuting Area 2010 primary codes from the Center for Disease Control & Prevention and US Department of Agriculture respectively, based on the zip code of residence. We extracted insurance status and history of comorbidities and prescriptions based on ICD-10-CM codes and Anatomical Therapeutical Classification codes prior to the date of inclusion (Supplementary Table 1).

Statistical analysis

Continuous variables were described using means (standard deviations) or medians (quartiles) as appropriate. Categorical variables were described using frequencies and percentages. Covariate balance after propensity score matching were assessed as standardized mean differences less than 20% [14]. Given that 35% of encounters did not have a weight measurement in the 6-to-9-month window when outcome was assessed, we constructed inverse probability weights for loss to follow-up [15]. We fitted marginal structural models to study the association of being prescribed incretin-based weight loss medications with changes in weight (kg), changes in percentage weight (percentage points), and achievement of at least 5% weight loss (risk ratio). We specify the target trial emulation design in Supplementary Table 2.

We conducted several sensitivity analyses to assess the robustness of our results. First, we studied if length of prescription of incretin-based weight loss medications was associated with differences in weight loss. Second, we studied if results differed after excluding those older than 75 years, by sex, or among patients with history of affective or psychosis disorders. Third, we studied if results were similar by incretin-based weight loss medication, relative to those prescribed neither.

RESULTS

The matched analytic sample consisted of 66,574 encounters when SGAs with 56% low, 35% intermediate, and 8% expected AIWG were prescribed, of which 13,319 involved prescription of semaglutide or tirzepatide (Table 1). The patients were on average aged 47.1 years (SD: 15.8), 83% female, 74% Non-Hispanic White, 13% Non-Hispanic Black and 6% Hispanic, with an average BMI of 39.5 kg/m^2 (SD: 7.7). Additional descriptive characteristics on comorbidities and medications are presented in Supplementary Table 4. The geographic distribution of the analytic sample is presented in Supplementary Fig. 3.

Follow-up information on body weight was available for 43,478 encounters, with 35.1% achieving at least 5% weight loss at 6 months among those prescribed semaglutide/tirzepatide, relative to 19.4% who were not. Encounters for which follow-up were available were similar to those lost to follow-up (Supplementary Table 4).

Compared to those who did not receive a prescription for incretin-based weight loss medication, receiving a prescription was associated with −2.80 kg (95% CI: −3.02, −2.58) and −2.72 percentage points (95% CI: −2.92, −2.51) decrease in weight. The latter were also 1.91 (Risk Ratio; 95% CI: 1.84, 1.99) times more likely to lose at least 5% of baseline weight. Results did not change after adjusting for all baseline covariates. Weight loss was greatest among patients prescribed low risk SGAs (−3.02 kg, 95% CI: −3.29, −2.74), followed by intermediate risk SGAs (−2.77 kg, 95% CI: −3.05, −2.40) and was the least for those prescribed high-risk SGAs (−1.33 kg, 95% CI: −2.04, −0.62) (Fig. 1).

Results did not differ by length of prescription (Supplementary Table 5), after excluding patients aged 75 years or older (Supplementary Table 6), and by sex (Supplementary Table 7). Weight loss was lower among individuals with history of psychosis disorders, compared to affective disorders (Supplementary Table 8). Prescription of semaglutide and tirzepatide were associated with −2.50 kg (95% CI: −2.73, −2.28) and −4.42 kg (95% CI: −4.97, −3.87) decrease in weight respectively (Supplementary Table 9).

DISCUSSION

In an analysis of the largest integrated database of electronic health records nationwide, we showed that prescription of

Table 1. Socio-demographic and clinical characteristics of analytic sample.

	Total	No prescription	Incretin-based weight loss medication prescription	SMD[a]
N	66,574	53,256	13,319	
Months to prescription of semaglutide or tirzepatide	–	–	1.1 (0.0, 2.0)	
SGA by risk of antipsychotic induced weight gain				
Low (+)	57%	57%	56%	1.16
Intermediate (++)	35%	35%	35%	0.08
High (+++)	8.3%	8.2%	8.7%	1.92
Age	47.1 (15.8)	47.1 (16.3)	47.2 (13.4)	0.42
Female	83%	83%	83%	1.83
Race ethnicity				
Non-Hispanic White	74%	74%	73%	2.18
Non-Hispanic Black	13%	13%	13%	0.61
Hispanic	6.0%	5.9%	6.3%	1.55
Non-Hispanic Other	6.9%	6.8%	7.6%	3.08
Social vulnerability index (0: lowest, 100: highest)	61.8 (35.5, 81.5)	61.8 (35.3, 81.5)	62.0 (36.0, 81.5)	0.51
Urban residence	92%	92%	92%	0.38
Insurance status				
Medicare	16%	16%	16%	0.90
Medicaid	27%	27%	28%	0.94
Other	79%	79%	79%	0.77
Weight (kg)	108.4 (23.8)	108.0 (23.9)	110.3 (23.4)	9.92
Body mass index (kg/m^2)	39.5 (7.7)	39.4 (7.7)	39.7 (7.3)	3.73
27.0–29.9 kg/m^2	9%	10%	6%	
30.0–34.9 kg/m^2	23%	23%	23%	
35.0–39.9 kg/m^2	25%	24%	27%	
≥40 kg/m^2	42%	42%	43%	

Values are reported as mean (SD) or median (25th percentile, 75th percentile) for continuous variables, or frequency (percentage) for categorical variables, for each encounter after propensity score matching. SGAs were categorized based on risk of antipsychotic induced weight gain (AIWG) as high (olanzapine, clozapine), intermediate (risperidone, quetiapine, paliperidone) and low (others).
[a]Standardized mean differences (absolute values).

semaglutide and tirzepatide was associated with clinically meaningful weight loss among individuals prescribed SGAs in 6 months. The magnitude of weight loss was the least among those receiving clozapine and olanzapine. Expected weight loss was higher among those prescribed tirzepatide, relative to semaglutide, consistent with randomized trials that did not include individuals prescribed SGAs [16].

We note that the magnitude of weight loss in this study was less than that observed in the general population with obesity or overweight from the randomized trials of incretin-based weight loss medications with lifestyle that report roughly 8–16% average weight loss in 6 months after initiation [16, 17]. However, our results are consistent with real-world effectiveness studies of these medications among people with and without type 2 diabetes that suggest lower rates of weight loss [18, 19]. There are several possible explanations for lower rates of weight loss in the study population such as counterregulatory metabolic effect of SGAs, insufficient access, shorter length of prescription, low adherence in our study population, and decreased effectiveness of from other obesogenic medications like antidepressants [20]. It is important to recognize that patients prescribed high AIWG-risk SGAs like clozapine can achieve meaningful weight loss in the context of a controlled research setting with close monitoring and structured support, as demonstrated recently in the COaST trial ($n = 31$) [21]. However, translating these outcomes to real-world practice may be more challenging.

This study has several strengths such as the large sample size and geographic representation of SMI cases. However, there were limitations. First, we did not have data on filled prescriptions and therefore do not know if the study population initiated or continued the prescription for the duration of the study, which may partially explain the lower observed weight loss compared to phase 3 trials. We did not have information on diet and physical activity, which may be worse relative to the general population, and may also explain the lower observed weight loss compared to trials. We did include the information on the dosage given shortages during the period of analysis. Second, given the nature of EHR data, the results are susceptible to information bias. Less than half of healthcare systems in the United States use Epic software and patients may have received incretin-based weight loss medication prescriptions from other health providers that do not contribute data to Epic Cosmos. Third, the analysis is also susceptible to confounding by indication such that patients prescribed SGAs resulting in high AIWG may have more complex clinical presentations. However, the stratified analyses by history of affective and psychosis disorders were consistent with the main analysis. Finally, although we used appropriate statistical approaches to account for loss to follow-up, nearly 40% of the analytic sample had missing data on body weight. However, this is unlikely to bias our results given similarities in patient characteristics by follow-up.

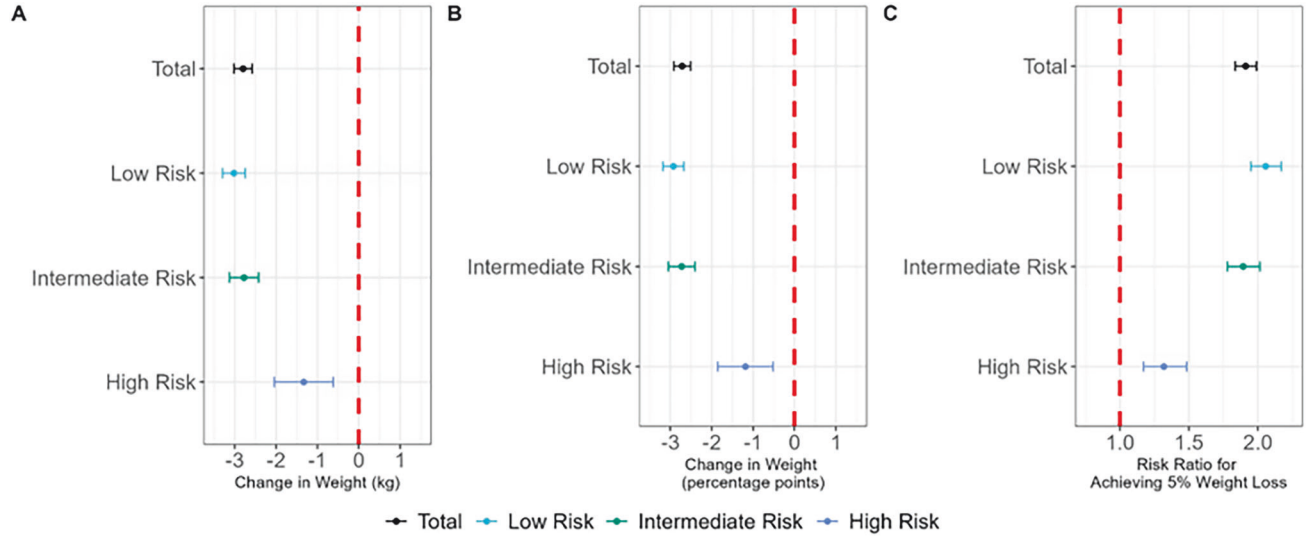

Fig. 1 Weight change 6 months after prescription of incretin-based weight loss medications by categories of second-generation antipsychotics. Associations (95% robust confidence intervals) are adjusted for baseline weight and duration of follow-up for prescription of incretin-based weight loss medications (semaglutide or tirzepatide). Second-generation antipsychotics were categorized based on their propensity for inducing weight gain as high (olanzapine, clozapine) intermediate (risperidone, quetiapine, paliperidone) and low (others). Panel **A** Weight (kg), Panel **B** Weight (percentage points), Panel **C** Risk ratio for 5% weight loss.

In summary, semaglutide and tirzepatide may be viable options for ameliorating weight gain in this vulnerable population, However, the expected weight loss from these medications may vary according to specific antipsychotic therapies.

DATA AVAILABILITY

The code for the analysis is available at https://github.com/chroniq-lab/cosmos-sga-bmi. Epic Cosmos access is available through institutional representatives of participating institutions and the Epic Cosmos team after completing certification requirements. Data were extracted in June 2024.

REFERENCES

1. Substance Abuse and Mental Health Services Administration. (2024). Key substance use and mental health indicators in the United States: Results from the 2023 National Survey on Drug Use and Health (HHS Publication No. PEP24-07-021, NSDUH Series H-59). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2023-nsduh-annual-national-report, https://www.samhsa.gov/data/sites/default/files/reports/rpt47095/National%20Report/National%20Report/2023-nsduh-annualnational.pdf.
2. Holt RIG. Association between antipsychotic medication use and diabetes. Curr Diab Rep. 2019;19:96. https://doi.org/10.1007/s11892-019-1220-8.
3. Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry. 2020;7:64–77. https://doi.org/10.1016/S2215-0366(19)30416-X.
4. Agarwal SM, Stogios N, Faulkner GEJ, Hahn M. Pharmacological interventions for the prevention of antipsychotic-induced weight gain in people with schizophrenia: a cochrane systematic review and meta-analysis. Schizophr Bull. 2023;49:833–5. https://doi.org/10.1093/schbul/sbad037.
5. Office of the Commissioner. FDA Approves new medication for chronic weight management. US Food and Drug Administration, Silver Spring, MD; 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-new-medication-chronic-weight-management.
6. Office of the Commissioner. FDA approves new drug treatment for chronic weight management, first since 2014. US Food and Drug Administration, Silver Spring, MD; 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014.
7. Moiz A, Levett JY, Filion KB, Peri K, Reynier P, Eisenberg MJ. Long-term efficacy and safety of once-weekly semaglutide for weight loss in patients without diabetes: a systematic review and meta-analysis of randomized controlled trials. Am J Cardiol. 2024;222:121–30. https://doi.org/10.1016/j.amjcard.2024.04.041.
8. Siskind D, Hahn M, Correll CU, Fink-Jensen A, Russell AW, Bak N, et al. Glucagon-like peptide-1 receptor agonists for antipsychotic-associated cardio-metabolic risk factors: a systematic review and individual participant data meta-analysis. Diabetes Obes Metab. 2019;21:293–302. https://doi.org/10.1111/dom.13522.
9. McElroy SL, Guerdjikova AI, Blom TJ, Mori N, Romo-Nava F. Liraglutide in obese or overweight individuals with stable bipolar disorder. J Clin Psychopharmacol. 2024;44:89–95. https://doi.org/10.1097/JCP.0000000000001803.
10. Larsen JR, Vedtofte L, Jakobsen MSL, Jespersen HR, Jakobsen MI, Svensson CK, et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: a randomized clinical trial. JAMA Psychiatry. 2017;74:719. https://doi.org/10.1001/jamapsychiatry.2017.1220.
11. Tarabichi Y, Frees A, Honeywell S, Huang C, Naidech AM, Moore JH, et al. The cosmos collaborative: a vendor-facilitated electronic health record data aggregation platform. ACI Open. 2021;05:e36–46. https://doi.org/10.1055/s-0041-1731004.
12. Nichols GA, Schroeder EB, Karter AJ, Gregg EW, Desai J, Lawrence JM, et al. Trends in diabetes incidence among 7 million insured adults, 2006–2011. Am J Epidemiol. 2015;181:32–9. https://doi.org/10.1093/aje/kwu255.
13. Yadav K, Lewis RJ. Immortal time bias in observational studies. JAMA. 2021;325:686. https://doi.org/10.1001/jama.2020.9151.
14. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med. 2013;32:3388–414. https://doi.org/10.1002/sim.5753.
15. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, Beck TL, Aggarwal NT, Wilson RS, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. Epidemiology. 2012;23:119–28. https://doi.org/10.1097/EDE.0b013e318230e861.
16. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387:205–16. https://doi.org/10.1056/NEJMoa2206038.
17. Ryan DH, Lingvay I, Deanfield J, Kahn SE, Barros E, Burguera B, et al. Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial. Nat Med. 2024. https://doi.org/10.1038/s41591-024-02996-7.
18. White GE, Shu I, Rometo D, Arnold J, Korytkowski M, Luo J. Real-world weight-loss effectiveness of glucagon-like peptide-1 agonists among patients with type 2 diabetes: a retrospective cohort study. Obesity. 2023;31:537–44. https://doi.org/10.1002/oby.23622.
19. Prasad F, De R, Korann V, Chintoh AF, Remington G, Ebdrup BH, et al. Semaglutide for the treatment of antipsychotic-associated weight gain in patients not responding to metformin—a case series. Ther Adv Psychopharmacol. 2023;13:20451253231165169. https://doi.org/10.1177/20451253231165169.
20. Petimar J, Young JG, Yu H, Rifas-Shiman SL, Daley MF, Heerman WJ, et al. Medication-induced weight change across common antidepressant treatments: a target trial emulation study. Ann Intern Med. 2024:M23-2742. https://doi.org/10.7326/M23-2742.

21. Siskind D, Baker A, Arnautovska U, Warren N, Russell A, DeMonte V, et al. Efficacy and safety of semaglutide versus placebo for people with schizophrenia on clozapine with obesity (COaST): a phase 2, multi-centre, participant and investigator-blinded, randomised controlled trial in Australia. Lancet Psychiatry. 2025;12:493–503. https://doi.org/10.1016/S2215-0366(25)00129-4.

ACKNOWLEDGEMENTS

We thank Meghan Howat of the Epic Cosmos Research team for their technical inputs. This manuscript is the result of funding in whole or in part by the National Institutes of Health (NIH) through a pilot grant from the Georgia Center for Diabetes Translation Research. It is subject to the NIH Public Access Policy. Through acceptance of this federal funding, NIH has been given a right to make this manuscript publicly available in PubMed Central upon the Official Date of Publication, as defined by NIH. Georgia Center for Diabetes Translational Research (P30DK111024).

AUTHOR CONTRIBUTIONS

JSV conceptualized the study with inputs from MKA, DRG, ROC and FJP. VRK and JSV had full access to the data in the study. JSV takes responsibility for the integrity of the data and the accuracy of the data analysis. JSV wrote the first draft. All authors reviewed and edited the subsequent drafts.

FUNDING

Georgia Center for Diabetes Translational Research Pilot Program (P30DK111024).

COMPETING INTERESTS

ROC has received research funding (to institution) from Otsuka, Karuna, Roche, and Alkermes. He is a consultant to IQVIA, Boehringer Ingelheim, and Syneos Health on behalf of the Clozapine Product Manufacturers Group. He is a speaker and consultant to Saladax Biomedical. MKA has served as a consultant for Eli Lilly. FJP has received research support through his institution from Dexcom, Tandem, Insulet, Novo Nordisk, and Ideal Medical Technologies, personal consulting fees from Dexcom, and has provided consulting services for Insulet (services paid to his institution). The authors declare no competing financial interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

We were exempt from ethical approval by the Emory University Institutional Review Board for the analysis of secondary data. All data in Epic Cosmos are HIPAA compliant and expert determined de-identified.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41366-025-01885-4.

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