Daniel Casillas
Final Paper
Pharmacoepidemiology PHOR 7615 001

Introduction

The rising prevalence of obesity among adolescents has prompted an urgent need for effective pharmacologic interventions. Over the past two decades, obesity rates among youth have nearly tripled, contributing to an increased risk for type 2 diabetes, cardiovascular disease, and orthopedic complications at earlier ages. Consequently, pharmacological therapies, once reserved primarily for adults, are increasingly being explored for pediatric populations.
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including agents such as semaglutide and liraglutide, have emerged as promising treatments for weight management and glycemic control in adults with obesity and diabetes. These medications exert their effects by enhancing insulin secretion, inhibiting glucagon release, delaying gastric emptying, and promoting satiety. However, the safety and efficacy of GLP-1 RAs during critical developmental windows such as adolescence remain poorly understood.

Puberty represents a unique and sensitive period marked by rapid skeletal growth, hormonal regulation, and metabolic adaptation. Intervening during this phase with pharmacological agents could theoretically alter natural growth trajectories, bone mineralization processes, and endocrine balances. While other side effects of GLP-1 RAs, such as nausea, vomiting, and appetite suppression, are well documented in adults, their potential long-term impacts on adolescents are less clear. Existing clinical trials in pediatric populations are relatively short in duration and often underpowered to detect subtle changes in growth or bone density. Thus, this study aims to address the following critical research question: Does GLP-1 receptor agonist therapy during adolescence impact growth outcomes, including height, bone mineral density, and metabolic health? Understanding these effects is vital for developing safe, evidence-based obesity treatment guidelines for youth.

Methods

Study Design
This study will employ a retrospective cohort design using large, real-world electronic health record (EHR) databases to track adolescents prescribed GLP-1 RAs compared to matched controls not receiving these medications. A retrospective design is particularly well-suited for studying relatively rare outcomes or for leveraging existing large datasets to identify associations that may not be feasible to study prospectively due to time and resource constraints.

Data Sources
Potential data sources include pediatric-focused networks such as PEDSnet, which aggregates data across major pediatric hospitals, and broader networks such as TriNetX and OptumLabs, which provide access to diverse patient populations across the United States. These databases provide longitudinal follow-up necessary for evaluating growth trajectories, laboratory values, and diagnoses over several years.

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Study Population
The study population will include adolescents aged 10 to 18 years who initiated GLP-1 therapy between 2015 and 2025. Eligibility criteria will require documentation of at least one year of medical records prior to initiation and a minimum of two years of follow-up. Controls will consist of adolescents matched on age, sex, race/ethnicity, baseline BMI percentile, and major comorbidities such as type 2 diabetes or hypothyroidism who did not receive GLP-1 therapy but may have undergone lifestyle counseling or alternative pharmacotherapy.

Exposure Measurement
Exposure will be defined as documented initiation of a GLP-1 RA, verified through pharmacy dispensing records, provider documentation, or direct medication administration records. Initiation dates and duration of therapy will be tracked to allow dose-response analyses where possible.

Outcome Measurement
Primary outcomes include the change in height-for-age Z-scores over a minimum two-year follow-up period, incidence of bone mineral density abnormalities (identified through DXA scans or surrogate markers), and changes in metabolic parameters such as HbA1c levels, lipid profiles, and insulin sensitivity indices. Secondary outcomes will include incident diagnoses of pancreatitis, thyroid disorders (including medullary thyroid carcinoma risk markers), and renal dysfunctions.

Covariates and Confounders
Potential confounders include baseline BMI percentile, Tanner stage (pubertal development), socioeconomic status indicators (insurance type, zip code-linked income data), and existing comorbidities such as polycystic ovarian syndrome (PCOS) or hypothyroidism. Behavioral factors such as baseline physical activity (if available) and dietary counseling records will also be considered where possible.

Unique Issues and Biases
Several unique biases may arise in this study. Confounding by indication remains a major concern, as adolescents prescribed GLP-1s may represent a sicker cohort compared to non-users. Selection bias may occur if patients who adhere to therapy differ systematically from those who discontinue. Measurement error could be introduced through reliance on EHR-entered anthropometric data, which may vary in quality across clinical sites. Additionally, loss to follow-up can skew results if dropouts differ systematically between exposed and unexposed groups.

Mitigation Strategies
Propensity score matching based on baseline characteristics will be employed to balance exposed and unexposed cohorts. Sensitivity analyses will be performed excluding participants with less than two years of follow-up. To address missing data, multiple imputation techniques will be used. Additionally, an instrumental variable analysis may be explored if an appropriate instrument can be identified (e.g., site-specific prescribing patterns).

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Statistical Methods

Multivariable linear regression will be the primary analytic approach to assess continuous outcomes (e.g., change in height Z-scores, bone density measurements). Logistic regression will be used for binary outcomes such as occurrence of pancreatitis or thyroid dysfunction. Time-to-event analyses (Kaplan-Meier survival curves and Cox proportional hazards models) will be conducted for outcomes such as time to diagnosis of significant metabolic or skeletal complications.

Power Consideration

Preliminary power calculations suggest that with approximately 500 adolescents exposed to GLP-1 therapy and 1,000 matched controls, the study will have 80% power to detect a 0.2 standard deviation difference in height-for-age Z-scores, assuming a two-sided alpha of 0.05. This sample size also provides reasonable power to detect clinically meaningful differences in bone mineral density and metabolic parameters.

Results

Given that preliminary analyses are ongoing, hypothetical results are considered.
If no significant differences in growth trajectories are observed between GLP-1 users and matched controls, this would suggest that GLP-1 therapy during adolescence does not adversely affect skeletal development, providing reassurance regarding their use in pediatric populations. Additionally, improvements in metabolic markers without detrimental effects on growth would strengthen the rationale for broader adoption of GLP-1 RAs in treating adolescent obesity.

Conversely, if GLP-1 use is associated with slower height velocity, decreased bone mineral density, or abnormal metabolic parameters, these findings would necessitate a reevaluation of the risk-benefit profile of GLP-1 therapy in adolescents. Such results would indicate that while GLP-1 RAs may offer metabolic benefits, they might also interfere with crucial aspects of growth and development, warranting more stringent monitoring and potentially restricting use to more severe cases or shorter durations.

Discussion

Should this study demonstrate no adverse impact on growth, it would align with limited emerging evidence suggesting that GLP-1 therapy is well tolerated among youth, and would provide critical support for integrating GLP-1 RAs into pediatric obesity treatment algorithms. This finding could encourage earlier intervention for adolescents with severe obesity, potentially preventing progression to adult comorbidities such as diabetes and cardiovascular disease.

However, if growth impairment is detected, it would suggest that GLP-1 therapies must be used with greater caution during critical developmental periods. It would highlight the need for

guidelines emphasizing regular monitoring of height, bone health, and endocrine function in adolescents receiving GLP-1 therapy. Furthermore, it would underline the importance of considering non-pharmacologic interventions as first-line therapy for adolescent obesity whenever feasible.

Public health implications are substantial. Adolescent obesity is not merely an individual clinical issue but a population-level public health crisis, with lifelong health and economic consequences. Safe, effective treatments could substantially impact health trajectories at a population scale. Conversely, unsafe interventions could create new long-term health challenges, exacerbating existing disparities.

Future research should prioritize prospective longitudinal studies with careful monitoring of growth parameters, bone health assessments, and hormonal profiles over multiple years. Subgroup analyses by sex, baseline BMI category, and pubertal stage should also be explored to identify populations at differential risk.

Conclusion

This proposed study seeks to fill a critical knowledge gap regarding the long-term safety of GLP-1 receptor agonists in adolescents. By leveraging large-scale, real-world data and robust pharmacoepidemiologic methods, this research will inform clinical practice guidelines and public health strategies, ultimately aiming to balance effective obesity management with the safeguarding of normal adolescent development. Regardless of the outcome, this study will contribute meaningfully to the evidence base guiding the appropriate use of GLP-1 RAs in vulnerable pediatric populations.

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