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Research Article

Evaluating Genetic Obesity Interventions: A Survival Analysis Approach

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Abstract

Background: Effective weight management is difficult when there is obesity, especially when genetic factors are involved. ***Objective***: This study evaluated the efficacy of three medications—Metformin, Ozempic (semaglutide), and Saxenda (liraglutide)—in promoting weight reduction. ***Methods***: A total of 165 participants were included in the study, with 70.9% classified as obese. Participants were treated with Metformin, Ozempic, or Saxenda, and their weight loss outcomes were monitored. Kaplan-Meier survival analysis was used to assess time-to-weight reduction, and Cox regression analysis was employed to identify predictors of weight loss. ***Results***: GLP-1 receptor agonists (Ozempic and Saxenda) demonstrated significantly greater weight reduction compared to metformin. Mean weight loss was 8.72 kg for Ozempic and 9.81 kg for Saxenda, compared to only 1.17–1.18 kg for Metformin. Kaplan-Meier analysis revealed that participants on Ozempic and Saxenda achieved weight reduction faster than those on Metformin. Cox regression analysis identified physical activity as the only significant predictor of weight reduction (HR=1.64, p=0.006), while age, diet, and smoking status were not statistically significant. ***Conclusions***: GLP-1 receptor agonists (Ozempic and Saxenda) are highly effective for weight reduction in individuals with obesity, particularly those with genetic predispositions, and should be considered as first-line treatments. Physical activity plays a critical role in enhancing weight loss outcomes and should be integrated into obesity management plans.

Keywords: Metformin, Obesity, Ozempic, Saxenda, Survival.

تقييم تدخلات السمنة الوراثية: نهج تحليل البقاء على قيد الحياة

الخلاصة

الخلفية: من الصعب إدارة الوزن بشكل فعال عندما تكون هناك سمنة، خاصة عندما تكون هناك عوامل وراثية. **الهدف**: قيمت هذه الدراسة فعالية ثلاثة أدوية - الميتفورمين، أوزيمبيك (سيماجلوتيد) ، وساكسيندا (ليراجلوتيد) - في تعزيز إنقاص الوزن. **أساليب**: تم تضمين ما مجموعه 165 مشاركا في الدراسة، تم تصنيف 70.9٪ منهم على أنهم يعانون من السمنة المفرطة. عولج المشاركون بالميتفورمين أو أوزيمبيك أو ساكسيندا، وتمت مراقبة نتائج فقدان الوزن لديهم. تم استخدام تحليل البقاء على قيد الحياة كابلان ماير لتقييم الوقت لتقليل الوزن، وتم استخدام تحليل انحدار كوكس لتحديد تنبؤات فقدان الوزن. **النتائج**: أظهرت ناهضات مستقبلات GLP-1 (Ozempic و Saxenda) انخفاضا أكبر في الوزن مقارنة بالميتفورمين. كان متوسط فقدان الوزن 8.72 كجم لأوزيمبيك و 9.81 كجم لساكسيندا ، مقارنة ب 1.17-1.18 كجم فقط للميتفورمين. كشف تحليل كابلان ماير أن المشاركين في Ozempic و Saxenda حققوا انخفاضا في الوزن بشكل أسرع من أولئك الذين تناولوا الميتفورمين. حدد تحليل انحدار كوكس النشاط البدني باعتباره المؤشر الوحيد المهم لفقدان الوزن (HR = 1.64 ، p = 0.006) ، في حين أن العمر والنظام الغذائي وحالة التدخين لم تكن ذات دلالة إحصائية. **الاستنتاجات**: ناهضات مستقبلات GLP-1 (Ozempic و Saxenda) فعالة للغاية في إنقاص الوزن لدى الأفراد الذين يعانون من السمنة ، وخاصة أولئك الذين يعانون من ميول وراثية ، ويجب اعتبارها علاجات من الخط الأول. يلعب النشاط البدني دورا مهما في تعزيز نتائج إنقاص الوزن ويجب دمجه في خطط إدارة السمنة.

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INTRODUCTION

Obesity is a global health challenge with profound social, economic, and medical consequences. The World Health Organization (WHO) identifies obesity as a significant contributor to non-communicable diseases, including cardiovascular disease, diabetes, and certain types of cancer [1]. While environmental and lifestyle factors, such as diet and physical inactivity, are well-established contributors to obesity, there is growing recognition of the role of genetic predisposition in its development. Genetic obesity is primarily characterized by mutations or variations in specific genes that regulate energy balance, appetite, and metabolism [2]. These genetic factors underline the importance of precision medicine approaches to manage and treat obesity effectively. Monogenic obesity, which results from single-gene mutations, has received a lot of attention among the genetic causes of obesity. Notably, changes in the melanocortin-4 receptor (MC4R) gene are the most common cause of monogenic obesity. They happen to about 2% to 5% of people who are severely obese [3]. Polygenic obesity, on the other hand, involves interactions between multiple genetic variants, each contributing modestly to an individual's risk. Advances in genomics have made it possible to identify these variants and their cumulative effects through

polygenic risk scores [4,5]. Pharmacological interventions targeting genetic pathways have emerged as a promising area of research. Drugs such as GLP-1 receptor agonists and MC4R agonists have demonstrated potential in weight management and improving metabolic outcomes. Moreover, understanding the interaction between genetic predisposition and environmental factors is critical for designing comprehensive treatment strategies [6]. This study aims to evaluate the effectiveness of these interventions using survival analysis, providing insights into their long-term impact on weight reduction and related comorbidities. Genetic, environmental, and behavioral factors all play a role in the multifactorial condition of obesity. Monogenic obesity results from rare, highly penetrated mutations in genes such as MC4R, LEPR, and POMC, which disrupt pathways regulating appetite and energy homeostasis [3]. These mutations often lead to severe early-onset obesity and are associated with hyperphagia and metabolic disturbances. New developments in genome-wide association studies (GWAS) have also found many genetic loci linked to polygenic obesity, highlighting the genetic complexity of the condition [2]. Pharmacological intervention includes the use of MC4R agonists, such as setmelanotide, specifically targeting the melanocortin pathway, and has shown significant efficacy in treating monogenic obesity. Studies report substantial weight loss and improvements in comorbidities among individuals with MC4R, LEPR, or POMC mutations [7]. GLP-1 receptor agonists, like liraglutide (Saxenda) and semaglutide (Wegovy), were first created to treat type 2 diabetes. They have since been shown to help people lose weight and improve their metabolism. These drugs act by enhancing satiety and reducing appetite, offering benefits for individuals with and without genetic predispositions [8]. Phentermine, an appetite suppressant, is often used as part of combination therapy to manage obesity. Although effective in short-term weight loss, its applicability for genetic obesity remains limited due to its nonspecific mechanism of action [9]. A biguanide derivative is a widely prescribed oral medication primarily used for the management of type 2 diabetes due to its ability to improve insulin sensitivity and reduce hepatic glucose production [10]. Beyond its glycemic control benefits, metformin has been associated with modest weight loss, particularly in individuals with insulin resistance or polycystic ovary syndrome (PCOS) [11,12]. While its weight loss effects are generally mild compared to newer anti-obesity medications, metformin remains a valuable therapeutic option due to its favorable safety profile, low cost, and additional metabolic benefits, such as reduced risk of cardiovascular events [13]. However, its efficacy in achieving significant weight reduction in individuals with genetic obesity remains limited, prompting the need for more effective pharmacological interventions [14]. While genetics play a crucial role, the interaction between genetic predisposition and environmental factors cannot be ignored. Lifestyle interventions, including dietary modifications and physical activity, are essential components of obesity management. Studies indicate that individuals with high genetic risk may derive greater benefits from structured lifestyle programs when combined with pharmacological treatments [15]. Despite advancements in pharmacogenetics, challenges remain in translating genetic insights into clinical practice. Limited access to genetic testing and variability in treatment responses highlight the need for personalized approaches. Future research should focus on integrating genetic, behavioral, and environmental data to develop comprehensive treatment strategies [2,16]. The interaction of genetics and pharmacology offers a promising method for addressing the obesity epidemic. By leveraging genetic insights and survival analysis, this study aims to contribute to the growing body of evidence supporting precision medicine approaches in obesity treatment. Survival analysis has been widely used to assess the long-term results of obesity treatments. Time-to-event data, like how long it takes to lose a lot of weight or get rid of other health problems, is often analyzed with Kaplan-Meier survival curves and Cox proportional hazards models [17]. These methods provide insights into the durability and efficacy of interventions, enabling comparisons across treatment modalities. This study aims to compare the efficacy of three pharmacological interventions—Metformin, Ozempic (semaglutide), and Saxenda (liraglutide)—in promoting weight reduction among individuals with obesity, particularly those with genetic predispositions. Additionally, the study sought to investigate the influence of lifestyle factors, such as physical activity, diet, age, and smoking status, on weight loss outcomes. By conducting survival analysis (Kaplan-Meier) and Cox regression modeling, the study aimed to identify predictors of successful weight reduction and determine the time-to-event differences among the treatment groups.

METHODS

Study design and setting

This study adopts a retrospective cohort design to evaluate the effectiveness of various interventions for genetic obesity using survival analysis for patients referring to the unit of obesity research at Al-Kindy College of Medicine. The study aims to compare the duration to clinically significant events (e.g., weight reduction milestones, comorbidity resolution, or treatment discontinuation) among patients receiving different interventions. The study was approved by the ethical committee of Al-Kindy College of Medicine. To minimize selection bias, a consecutive sampling method was used to include all eligible patients who met the inclusion criteria during the study period at Al-Kindy Unit of Obesity Research. This approach ensured that no selective inclusion or exclusion occurred beyond predefined criteria. To reduce recall bias, primary data were extracted directly from medical records, which included physician-documented clinical notes, laboratory results, and intervention histories. Self-reported data (e.g., lifestyle habits or dietary compliance) were used only

when documented in the medical file and were corroborated by clinical follow-up notes when possible.

Inclusion criteria

The study includes individuals diagnosed with genetic obesity, identified through clinical evaluations (as assessed by specialists at Al-Kindy College of Medicine/Unit of Obesity Research).Eligibility criteria include the history of using one or more obesity interventions (pharmacological or lifestyle-based) for at least 6 months, age ≥18 years, and no prior bariatric surgery or concurrent experimental treatments.

Exclusion criteria

Patients without follow-up data or with contraindications to the treatments are excluded.

Sampling and recruitment

Participants were identified through a retrospective review of medical records from Al-Kindy Unit of Obesity Research between March 2022 and July 2024. A consecutive sampling method was used, including all eligible patients who were seen during the study period and met the inclusion criteria.

Data collection

Data were collected from healthcare records and patient-reported outcomes using a structured questionnaire previously distributed to the public. The questionnaire included demographic information (age, sex, and BMI at baseline), lifestyle habits (diet, smoking status, and physical activity), and details about treatments used (treatment type, duration, and time to weight reduction). Weight was defined as ≥10% loss of baseline body weight sustained for at least 3 months, as documented in follow-up records. Adherence to dietary intervention was defined based on clinician notes and patient reports. Documentation of dietary adherence was extracted from follow-up consultations. Physical activity status was classified as active if the patient reported engaging in ≥150 minutes of moderate-intensity aerobic activity per week, as per WHO guidelines, or inactive if below this threshold. This was based on self-reports recorded in clinic notes or questionnaires. Smoking Status: Information smoking status was obtained from interviews intake and verified in follow-up notes.

Data analysis

Means, medians, and percentages are summarized, and comparisons of treatment groups using chi-square tests for categorical variables and t-tests/ANOVA for continuous variables. Survival curves for time-to-event outcomes stratified by intervention type using Kaplan-Meier analysis. Log-rank test to compare survival distributions across treatment groups. Cox regressions were used to analyze the hazards model of multivariable analysis to adjust for confounders (e.g., age, diet, and smoking status). Hazard ratios (HRs) with 95% confidence intervals to identify the impact of each intervention on survival probabilities. Data were analyzed using SPSS software V28. Kaplan-Meier and Cox regression models were built using the survival analysis module in SPSS. The hazard function in Cox regression models the instantaneous risk of an event (e.g., in this study it is achieving weight reduction) occurring at a given time (t), conditional on the individual having survived (not experienced the event) up to that time. The hazard function is expressed as:

$$h(t)=h0(t)\cdot\exp(\beta1X1+\beta2X2+\cdots+\beta pXp) \text{ ---- eq.1}$$

Where: $h(t)$= the hazard at time (t), representing the instantaneous risk of the event occurring at that time. $h0(t)$= the baseline hazard function, which describes the hazard when all predictor variables (X1, X2, …, Xp) are zero. $\beta1, \beta2\ldots. \beta p,$ the regression coefficients corresponding to the predictor variables (X1, X2, ……., Xp). X1, X2, ….. Xp, the predictor variables (e.g., age, diet, physical activity, smoking status).

Covariates (e.g., age, diet, smoking) were chosen a priori based on biological plausibility and prior literature. No automated selection methods (e.g., stepwise) were used to avoid overfitting. Statistical significance was defined as a $p< 0.05$, indicating that the observed results were unlikely to have occurred by chance. This threshold was used to determine the significance of associations and differences in the analysis.

RESULTS

The study included a total of 165 participants, with a mean age of 46.36±9.62 years. The sample comprised 134 (81.2%) females and 31 (18.8%) males. Most participants identified as obese (70.9%). Table 1 summarizes the demographic characteristics of the study population. Among the variety of interventions used in managing genetic obesity, the participants dominantly used three medications. GLP-1 receptor agonists—Ozempic (semaglutide) and Saxenda (liraglutide)—in addition to metformin**,** were evaluated for their efficacy and safety in managing. Ozempic, administered as a once-weekly subcutaneous injection, was utilized for its glucose-lowering effects and weight management benefits, with participants receiving a dose escalation up to 1.0 mg. Saxenda, a daily injectable liraglutide formulation, was employed primarily for weight management, with doses titrated to 3.0 mg as tolerated. Metformin, an oral medication, served as a comparator or adjunct therapy due to its established role in improving insulin sensitivity and glycemic control. Participants were asked for side effects and clinical outcomes, including changes in body weight, as shown in Table 2.

Table 1: Demographic characteristics of the participants

Variable		Frequency (%)
Gender	Female	134(81.2)
	Male	31(18.8)
BMI rank	Normal weight	3(1.8)
	Overweight	45(27.3)
	Obese	117(70.9)
Smoking status	Non-smoker	145(87.9)
	Smoker	20(12.1)

Table 2: Treatment, outcomes, and side effects distribution

Variable		Frequency
Treatment type	Metformin	35(21.2)
	Ozempic	47(28.5)
	Saxenda	83(50.3)
Weight reduction, >10%	No.	19(11.5)
	Yes	146(88.5)
Diet	Normal	32(19.4)
	Low carb	41(24.8)
	Calorie controlled	92(55.8)
Physical activity	Sedentary	93(56.4)
	Moderate activity	72(43.6)
Side effects	No	96(58.2)
	Epigastric pain	19(11.5)
	Diarrhea	16(9.7)
	Gastric upset	15(9.1)
	Hypoglycemia	19(11.5)

Metformin has been shown to contribute to weight loss, but its effect is less pronounced compared to medications like Ozempic (semaglutide) or Saxenda (liraglutide). Also, the results show that these GLP-1 receptor agonists and metformin have very different effects on weight loss, with a difference that is statistically significant ($p<0.001$), as shown in Table 3. The Kaplan-Meier analysis was used to assess the time (in weeks) required to achieve weight reduction across the treatment groups (Metformin, Ozempic, and Saxenda). In this analysis, the event of interest was defined as the achievement of weight reduction, while censored cases represented individuals who did not achieve weight reduction during the study period, as illustrated in Figure 1. The log-rank test revealed that the differences in the time to weight reduction among the treatment groups were statistically significant ($p< 0.001$), highlighting the varying efficacy of Metformin, Ozempic, and Saxenda in promoting weight loss over time. To further explore the influence of relevant covariates—such as age, diet, physical activity, and smoking status—on weight loss and to quantify their associated hazard ratios, a Cox regression analysis was conducted. The results indicated that physical activity is the only factor significantly contributing to weight reduction, with a statistically significant hazard ratio.

Table 3: Distribution of participants according to the treatments used

Treatment type	Gender	n(%)	Weight (kg)			*p*-value
			Before treatment	After treatment	Difference	
Metformin	Female	18(10.91)	76.56±7.78	75.39±7.26	1.17±2.46	<0.001
	Male	17(10.30)	76.18±8.21	75±7.38	1.18±1.74	
Ozempic	Female	39(23.64)	89.77±5.30	81.05±7.53	8.72±7.8	
	Male	8(4.85)	95.25±7.57	87±9.13	8.25±3.15	
Saxenda	Female	77(46.67)	88.60±6.25	78.79±8.22	9.81±6.44	
	Male	6(3.64)	97.83±2.04	91±2.04	6.83±2.04	

Values were expressed as number, percentage, and mean±SD.

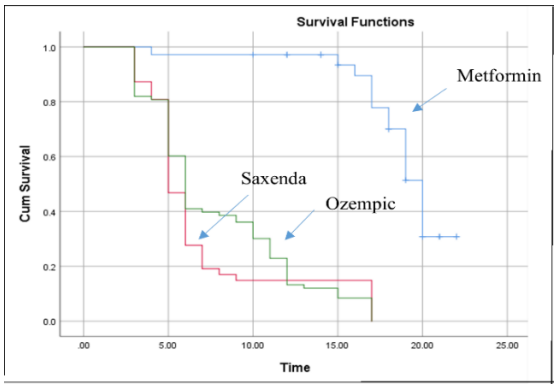

Figure 1: Survival function of the treatments used in the study.

In contrast, the effects of age, diet, and smoking status were found to be statistically insignificant, as detailed in Table 4. This suggests that, among the factors examined, physical activity plays the most critical role in promoting weight loss, while the contributions of age, diet, and smoking status remain inconclusive in this analysis. Using the coefficients (B) from the Cox regression results, the hazard function can initially be expressed as:

$h(t)=h0(t)\cdot\exp(0.003\cdot Age+0.041\cdot Diet+0.495\cdot Physical\ activity+0.731\cdot Smoking)$ … eq. 2

However, after excluding the statistically insignificant covariates (age, diet, and smoking status), the equation simplifies to:

$h(t)=h0(t)\cdot\exp(0.495\cdot Physical\ activity)$ ….. eq. 3

This modified equation highlights that physical activity is the only significant predictor of weight reduction in this analysis, with a hazard ratio of $\exp(0.495) = 1.64$, indicating a 64% increase in the likelihood of weight reduction for individuals engaging in physical activity compared to those who do not. The model is statistically significant ($p< 0.05$).

Table 4: Coefficients of the hazard equation

Variable	B	(HR)	*p*-value	95% CI
Age (year)	0.003	1.003	0.772	0.983–1.023
Diet	0.041	1.042	0.870	0.638–1.701
Physical activity	0.495	1.641	0.006	1.15–2.34
Smoking	0.731	2.077	0.052	0.996–4.33

DISCUSSION

The findings of this study provide an insight into the effectiveness of different treatments for weight reduction in individuals with obesity, particularly those with genetic predispositions. The study

population consisted of 165 participants, predominantly female (81.2%), with a mean age of 46.36 years. Most participants were obese (70.9%), reflecting the high prevalence of obesity in the study sample [18,19]. This demographic profile is consistent with other studies that highlight the higher prevalence of obesity in middle-aged populations and the increasing burden of obesity-related comorbidities [20]. The predominance of females in the study aligns with findings from other obesity studies, where women are often more likely to seek weight management interventions [21]. The high percentage of obese individuals underscores the need for effective treatments tailored to this population [22]. The study evaluated three medications: metformin, Ozempic (semaglutide), and Saxenda **(**liraglutide**)**. The differences in weight reduction between metformin and GLP-1 receptor agonists were statistically significant ($p< 0.001$). These medications were chosen for their established roles in weight management and glycemic control [10] and because the participants used these medications over other types of weight-reduction interventions. While metformin is primarily used for glycemic control in type 2 diabetes, it also demonstrated modest weight loss effects in this study (mean weight reduction of 1.17–1.18 kg). This aligns with previous studies showing that metformin leads to mild weight loss, particularly in individuals with insulin resistance [11]. Additionally, Ozempic and Saxenda, both GLP-1 receptor agonists, showed significantly greater weight reduction compared to Metformin. Ozempic resulted in a mean weight loss of 8.72 kg in females and 8.25 kg in males, while Saxenda led to a mean weight loss of 9.81 kg in females and 6.83 kg in males. These findings are consistent with clinical trials demonstrating the superior efficacy of GLP-1 receptor agonists in promoting weight loss, with reductions of 5–15% of body weight [23,24]. The results support the growing evidence that GLP-1 receptor agonists are more effective than traditional medications like metformin for weight management, particularly in individuals with obesity. This is consistent with studies such as the STEP trials for semaglutide and the SCALE trials for liraglutide, which highlight their role in achieving clinically significant weight loss [25,26]. While GLP-1 receptor agonists (e.g., Ozempic, Saxenda) are generally more effective than metformin for weight loss, some studies report variability or contradictory results. For instance, not all participants achieve significant weight reduction with GLP-1 agonists, and weight regain after discontinuation is common [23,25]. Similarly, metformin's weight loss effects are more pronounced in individuals with insulin resistance, with minimal benefits observed in non-diabetic populations [11,27]. Differences in outcomes may arise due to genetic variability, adherence, tolerability, and baseline metabolic health [26,28]. These discrepancies highlight the importance of personalized treatment approaches and combining pharmacological interventions with lifestyle modifications to optimize weight loss outcomes. The Kaplan-Meier analysis showed that the time it took to lose weight was significantly different between treatment groups ($p< 0.001$). People taking Saxenda (liraglutide) and Ozempic (semaglutide) lost weight faster than people taking Metformin. This aligns with the rapid onset of action of GLP-1 receptor agonists, which have been shown to produce significant weight loss within the first 12–16 weeks of treatment [23,24]. Similar findings have been reported in studies such as the SUSTAIN and LEAD trials, which demonstrated early and sustained weight loss with GLP-1 receptor agonists compared to other treatments [25,26]. However, some studies have reported variability in the time to weight reduction, with factors such as adherence, baseline weight, and genetic differences influencing outcomes [29,30]. These discrepancies highlight the need for personalized treatment approaches and further research to identify predictors of rapid and sustained weight loss with GLP-1 receptor agonists. The Cox regression analysis identified physical activity as the only significant predictor of weight reduction (HR= 1.64, $p= 0.006$). This highlights the importance of lifestyle modifications, particularly exercise, in enhancing the effectiveness of pharmacological treatments for obesity. The role of physical activity in weight management is well-documented. Studies have shown that combining pharmacotherapy with lifestyle interventions, such as increased physical activity, leads to better weight loss outcomes compared to medication alone. For example, a 2019 study by Jakicic *et al*. [31] found that individuals who engaged in regular physical activity while taking weight loss medications achieved greater weight reduction than those who relied solely on medication. On the other hand, age, diet, and smoking were not statistically significant in this study, which contrasts with some previous research. Dietary interventions are key to weight management. However, the lack of significance in this study may be due to the heterogeneity of dietary patterns, the relatively small sample size, or genetic factors. The simplified hazard function {$h(t)=h0(t)\cdot\exp(0.495\cdot$Physical activity; equation 3} highlights the critical role of physical activity in weight reduction. The hazard ratio of 1.64 indicates a 64% increase in the likelihood of achieving weight reduction for individuals who engage in physical activity. This finding is consistent with studies emphasizing the synergistic effects of combining pharmacotherapy with physical activity. For example, a 2020 study by Swift *et al*. [32] demonstrated that individuals who adhered to both medication and exercise regimens achieved significantly greater weight loss than those who did not. The results of this study highlight the superior efficacy of GLP-1 receptor agonists (Ozempic and Saxenda) over metformin for weight reduction in individuals with obesity. Additionally, physical activity emerged as a significant predictor of weight loss, reinforcing the importance of lifestyle modifications in obesity management. These findings align with existing literature and support the use of GLP-1 receptor agonists as first-line treatments for obesity, particularly when combined with physical activity. Future research should explore the long-term sustainability of these interventions and the role of

personalized treatment approaches based on genetic and lifestyle factors.

Study limitations

Due to the retrospective design nature of the study, there is potential for selection bias. Furthermore, the reliance on self-reported data introduces the possibility of recall bias.

Conclusion

The findings demonstrated that GLP-1 receptor agonists (Ozempic and Saxenda) were significantly more effective than metformin in achieving weight loss. Moreover, the results highlighted the superior efficacy of GLP-1 receptor agonists for weight management. This was supported by the Kaplan-Meier survival analysis, which showed that people taking Ozempic and Saxenda lost weight faster than people taking Metformin, with big differences in the time it took for events to happen. This aligns with the rapid and sustained weight loss observed in clinical trials of GLP-1 receptor agonists. Additionally, the Cox regression analysis identified physical activity as the only significant predictor of weight reduction, emphasizing the importance of lifestyle modifications in enhancing the effectiveness of pharmacological treatments. In contrast, age, diet, and smoking status did not show statistically significant effects on weight loss in this study.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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