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SHORT REPORT

Translational Physiology

Heart and health behavior responses to GLP-1 receptor agonists: a 12-wk study using wearable technology and causal inference

Gregory J. Grosicki,[1] Jeongeun Kim,[2] Finn Fielding,[2] Summer R. Jasinski,[2] Christopher Chapman,[2] William von Hippel,[2,3] and Kristen E. Holmes[2]

[1]*Scienceye, Bluffton, South Carolina, United States;* [2]*Performance Science, WHOOP Inc., Boston, Massachusetts, United States; and* [3]*Research with Impact, Brisbane, Queensland, Australia*

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were originally developed for the treatment of type 2 diabetes but have recently been approved for chronic weight management and reducing cardiovascular risk in individuals with overweight and obesity. Despite this approval, significant heterogeneity in the cardioprotective benefits and less desirable increases in resting heart rate (RHR) with GLP-1 RAs have been reported. To better understand cardiovascular responses to GLP-1 RAs and the potential role of health behaviors in influencing these responses, we leveraged wearable technology and causal inference analysis. We tracked RHR, heart rate variability (HRV), physical activity, and sleep in 66 individuals (42 ± 9 yr, body mass index: 30.0 ± 7 kg/m^2) from the week before to 12 wk following the initiation of GLP-1 RA medication. Propensity score matching on a larger sample of wearable users identified a control group with similar anthropometric and cardiovascular characteristics (Ps > 0.26). After the 12-wk study period, GLP-1 users showed significant (Ps < 0.05) weight loss (−10.0%, 95% CI: −11.2% to −8.5%) and changes in RHR (3.2 ± 0.8 beats/min) that were mediated ($P < 0.01$) by changes in HRV (−6.2 ± 1.4 ms) compared with control. Trends (Ps < 0.10) suggested that increases in weekly physical activity were associated with GLP-1 RA medication (31.5 ± 13.2 min) and that higher physical activity levels accompanied an attenuation of RHR increases. Our real-world findings align with clinical trial data in showing rapid and significant weight loss with GLP-1 RAs, coinciding with increases in RHR that are mediated by changes in autonomic function (i.e., HRV). Physical activity may help to offset RHR increases, but further research is needed to confirm these effects.

NEW & NOTEWORTHY These findings are among the first to provide daily insights into cardiovascular and behavioral responses following GLP-1 RA initiation. Substantial weight loss and significant increases in resting heart rate mediated by reductions in heart rate variability during the initial 12 wk of GLP-1 RA therapy were observed. In addition, trends suggest an increase in physical activity with GLP-1 therapy, and that physical activity may help to temper GLP-1 RA-associated increases in resting heart rate.

anti-obesity medication; heart rate; heart rate variability; obesity; physical activity

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) were originally developed for the treatment of type 2 diabetes but have recently been approved for chronic weight management and reducing cardiovascular risk in individuals with overweight and obesity. GLP-1 RAs delay gastric emptying and promote feelings of satiety, leading to weight loss that surpasses what is achieved with lifestyle intervention alone or earlier weight loss medications (1, 2). Intriguingly, GLP-1 RAs provide cardiometabolic benefits beyond weight loss, such as reductions in blood pressure (3) that occur despite less desirable increases in resting heart rate (RHR) (4). However, significant heterogeneity in GLP-1 RA cardiovascular outcome trials has been observed (5).

Wearable technology offers an attractive approach to better understand cardiovascular responses to GLP-1 RAs by enabling continuous monitoring of cardiovascular health outside the clinic or laboratory environment. Moreover, wearable tracking of health behaviors, such as physical activity and sleep, may provide unique insights into moderators of these cardiovascular responses and inform strategies to mitigate RHR increases and optimize the cardioprotective benefits of GLP-1 RAs. Unlike tightly controlled clinical trials, this real-world approach captures data in everyday settings, offering a more practical understanding of interactions between GLP-1 RAs, cardiovascular health, and health behaviors.

Correspondence: K. E. Holmes (holmes@whoop.com); G. J. Grosicki (gjgrosicki@gmail.com).
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In this real-world evidence study, we leveraged longitudinal measurements, wearable technology, and causal inference to examine changes in cardiovascular measures [RHR, heart rate variability (HRV), and respiratory rate (RR)] and health behaviors (physical activity and sleep) during the initial 12 wk of GLP-1 RA therapy. We hypothesized that GLP-1 RAs would increase RHR (4) and reduce HRV and RR (6, 7), with these effects on RHR and HRV attenuated by regular physical activity and healthy sleep patterns.

MATERIALS AND METHODS

Data Collection

Participants consented to their anonymized data being used for research purposes. Responses to a one-time survey delivered through the WHOOP (Boston, MA) mobile application on April 16, 2024 were collected to gather demographic details and information about body mass changes from individuals indicating GLP-1 RA use over their initial 12 wk of therapy.

Cardiovascular metrics, physical activity, and sleep data for this analysis were collected from participants between November 7, 2023 and April 16, 2024 using a wearable device (WHOOP strap 4.0, Boston, MA). The WHOOP strap continuously collects heart rate (via photoplethysmography) and accelerometry (via three-axis accelerometer) data. Cardiovascular metrics of interest including RHR, HRV, and RR were calculated as a weighted average from the primary sleep episode. HRV was calculated using the root mean square of successive differences (RMSSD) (8). Physical activity metrics included the amount of time spent in four physical activity zones, classified as a percentage of age-predicted heart rate maximum (9): light (zone 2: 60%–70%), moderate (zone 3: 70%–80%), hard (zone 4: 80%–90%), and max (zone 5: 90%–100%). Nightly sleep duration was also measured. The WHOOP cardiovascular and sleep measures have been validated in a general population against gold-standard electrocardiogram and polysomnography measures with a low degree of bias and low precision of errors (10, 11). Because data were not identifiable and were stored on a secure server, this study (No. 24074) was deemed exempt from Institutional Review Board oversight by Salus's IRB (Austin, TX).

Inclusion Criteria

Survey responses from individuals 21 yr of age or older who reported at least 12 wk use of GLP-1 medication were considered for the study. All participants were asked to self-report their sex as male, female, nonbinary, or prefer not to say by the WHOOP smartphone application. Member survey responses were paired with wearable data for the week before (i.e., baseline) and the 12 wk following GLP-1 RA therapy initiation. As our primary interest was change in cardiovascular metrics from baseline to *week 12*, eligibility was conditional on a minimum of 3 days of data for these weeks (i.e., baseline and *week 12*) and five additional weeks between baseline and *week 12* (i.e., at least 6 of 12 wk total). In the case that baseline data were unavailable, the week prior was considered. If baseline data availability was still an issue the participant was excluded. Cardiovascular metrics, physical activity, and sleep habits for each week were characterized by averaging data over the preceding 7-day window.

Propensity Score Matching for Causal Inference

We used propensity score matching to identify a comparable cohort of WHOOP members who did not use GLP-1 RA therapy. A total of 391,341 WHOOP members with data availability that satisfied the inclusion criteria during the same window of time as our GLP-1 cohort were considered. Propensity scores were calculated using the R "MatchIt" package. We used a logistic regression model with treatment assignment [GLP-1 vs. members not using GLP-1s or any other form of weight loss medication (Control)] as the dependent variable. Independent variables included age, sex, height, weight, and baseline RHR, HRV, and RR. These characteristics were chosen to ensure that matched cohorts would exhibit comparable baseline physiological profiles. Participants were matched using a 1:1 nearest neighbor matching algorithm. This method allows for the creation of a control group with similar baseline characteristics as the GLP-1 users, thereby strengthening the causal inference of GLP-1 RA effects on cardiovascular measures in the studied population.

Statistical Analysis

Statistical analyses were conducted using R (version 4.4.0). Outliers, defined as values beyond 1.5 times the interquartile range (IQR) from Q1 or Q3, were excluded. Participant descriptive characteristics are presented as means ± standard deviation (SD), and normality was assessed via the Shapiro–Wilk test and quantile-quantile plots. Independent t tests compared baseline characteristics between GLP-1 and Control groups.

Linear mixed models (LMMs) assessed changes in body mass and cardiovascular measures over time, with fixed effects for time, group (GLP-1 vs. Control), and their interaction, and random effects for participants. Tukey's post hoc tests explored group differences at specific time points. Additional LMMs examined associations between weight change and cardiovascular measures at *week 12*, adjusting for baseline values of the respective measures. Causal mediation analysis (1,000 bootstrap simulations) tested whether HRV changes mediated the effect of GLP-1 RAs on RHR changes.

Physical activity and sleep duration differences between groups over time were analyzed through separate LMMs. Physical activity was represented as the sum of the total time spent in each activity zone, with higher-intensity activities (zones 4 and 5) weighted by a factor of two. We also tested associations between changes in physical activity and weight at *week 12*, adjusting for baseline weight.

To investigate whether physical activity or sleep duration moderated cardiovascular responses to GLP-1 treatment, an analysis of covariance was conducted. GLP-1 users were divided into low- and high-activity/sleep groups using a median split based on averages over the 12-wk period. Models were fitted with *week 12* RHR or HRV as the outcome and group (low vs. high) as the independent variable, adjusting for baseline RHR or HRV. Statistical significance was set at $\alpha \leq 0.05$.

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RESULTS

Participant Characteristics

The study included 132 participants, evenly divided between the GLP-1 ($n = 66$) and Control ($n = 66$), with the Control group selected through propensity score matching. Presented as GLP-1 versus Control, groups were comparable by sex (38 males, 27 females, 1 nonbinary vs. 42 males, 24 females; $P = 0.50$), age (42.4 ± 8.9 vs. 43.0 ± 11.0 yr; $P = 0.74$), height (1.7 ± 0.1 m vs. 1.7 ± 0.1 m; $P = 0.47$), weight (87.7 ± 23.5 vs. 83.5 ± 18.9 kg; $P = 0.26$), and body mass index (BMI; 30.0 ± 6.6 vs. 29.1 ± 5.5 kg/m^2; $P = 0.39$). Resting cardiovascular metrics, including resting heart rate (67.1 ± 9.6 vs. 67.5 ± 8.5 beats/min; $P = 0.83$), heart rate variability (38.5 ± 16.4 vs. 37.4 ± 17.1 ms; $P = 0.69$), and respiratory rate (16.0 ± 1.6 vs. 15.8 ± 1.4 breaths/min; $P = 0.44$), were similarly balanced.

The number of days per week that participants wore the device was relatively similar between the GLP-1 and Control groups (6.2 ± 0.6 vs. 6.5 ± 0.9 days/wk), as was the proportion of weekday (71.4 ± 0.03 vs. 72.1 ± 0.02%) and weekend (28.6 ± 0.03 vs. 27.9 ± 0.02%) wear (*P*s = 0.06).

Weight Loss and Cardiovascular Responses to GLP-1 RA Therapy

At *week 12*, 43 participants self-reported their body weight, 2 of which were identified as outliers (−29.8% and −58.7%) and removed from analysis. Among the remaining 41 participants in the GLP-1 group, the mean relative body weight change was −10.0% (95% CI: −11.2% to −8.7%) and 90.2% of participants achieved a weight loss of ≥5% of their total initial body weight. Significant differences in relative body weight change were detected across time points ($P < 0.001$; Fig. 1).

Cardiovascular measures by group over time are visualized in Fig. 2. A significant group × time interaction was observed for both RHR and HRV (*P*s = 0.01). Post hoc testing indicated that HRV was significantly reduced in the GLP-1 compared with the Control group at 4-, 8-, and 12-wk time points (*P*s ≤ 0.05; Fig. 2*A*). At *week 12*, HRV was 6.2 ± 1.4 ms lower in the GLP-1 versus Control group. For RHR, significant increases were observed in the GLP-1 group at 8 and 12 wk compared with the Control group (*P*s < 0.01; Fig. 2*B*), and RHR was 3.2 ± 0.8 beats/min greater in GLP-1 versus Control group at *week 12*. The association between GLP-1 therapy and RHR and HRV changes was confirmed through sensitivity analyses, which revealed a significant effect of time (i.e., Baseline vs. 12 wk) on these outcomes within the GLP-1 group (*P*s < 0.01). Respiratory rate showed no significant group × time interactions or main effects (*P*s > 0.23; data not shown).

Moderators and Mediators of Cardiovascular Responses to GLP-1 Therapy

Weight loss was marginally associated with an increase in RHR ($P = 0.07$); for each 1% decrease in body weight, RHR was estimated to increase by 0.33 ± 0.17 beats/min. However, weight loss was not associated with changes in HRV ($P = 0.21$).

Mediation analysis demonstrated that changes in HRV mediated 72.4% of the total effect of GLP-1 therapy on RHR ($P < 0.01$). The total effect of GLP-1 therapy on RHR was 3.42 beats/min (95% CI: 1.5–5.2 beats/min; $P < 0.01$), whereas the average causal mediation effect via HRV change was 2.47 beats/min (95% CI: 1.2–3.9 beats/min; $P < 0.01$). After accounting for HRV changes, the direct effect of GLP-1 therapy on RHR was not significant (95% CI: −0.62 to 2.41 beats/min; $P = 0.26$).

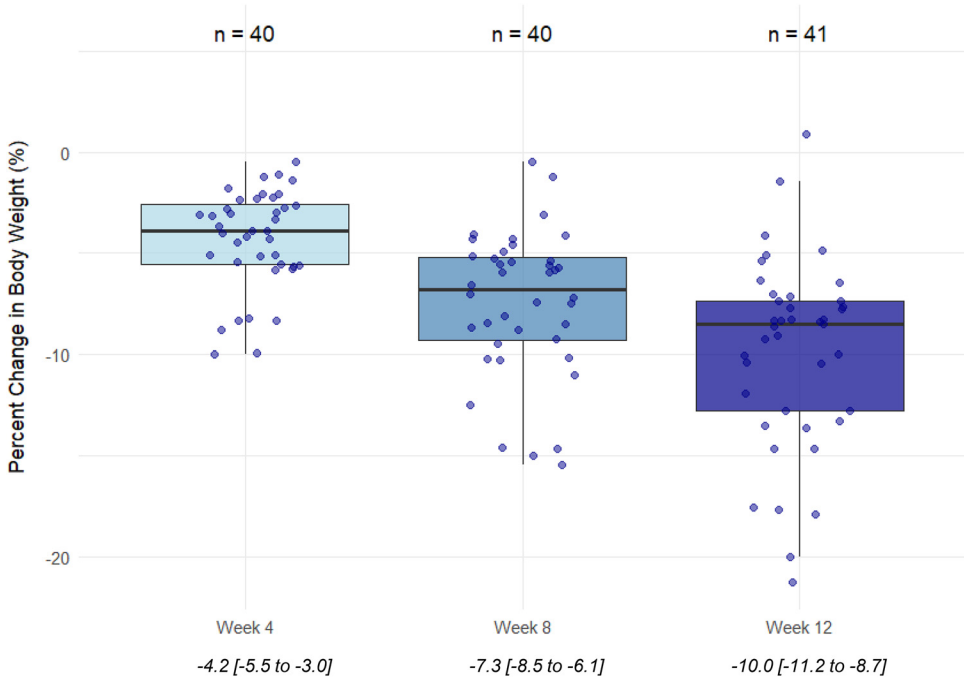


Figure 1. Relative body weight change (% change) in the glucagon-like peptide-1 (GLP-1) group at *weeks 4*, *8*, and *12*. Boxplots show the distribution of data points at each time point, with individual participant data displayed as dots to show variability within each group. The sample size at each time point is shown above the plots. The median and corresponding 95% confidence interval are provided below each time point.

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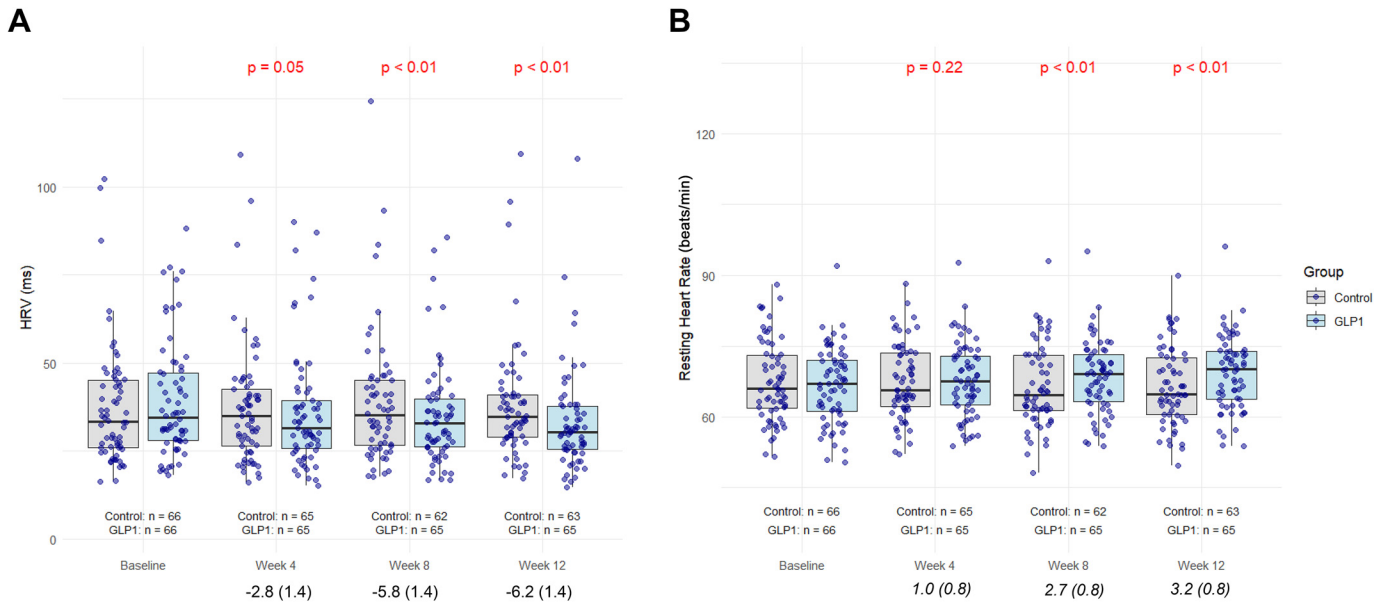


Figure 2. Changes in heart rate variability (HRV; *A*) and resting heart rate (RHR; *B*) across time in Control and GLP-1 groups. Boxplots show the distribution of data at each time point, with individual participant data displayed as dots to show variability within each group. The mean change and the corresponding standard error are provided below each time point. The sample size at each time point is shown below the plots. The *P* values above come from post hoc hypothesis testing between groups at each time point.

GLP-1 RA Therapy and Health Behaviors

Physical activity and sleep duration measures by group and time are visualized in Fig. 3. In the model for physical activity, the *P* value for the group × time interaction was 0.09 (Fig. 3*A*). Post hoc comparisons showed an average change of −7.3 ± 13.4 min in Control ($P = 0.67$) versus a 31.5 ± 13.2 min change in the GLP-1 group ($P = 0.08$). A median split of the GLP-1 group based on average daily physical activity (9.7 min/day) revealed a trend, suggesting that higher physical activity participation was associated with an attenuation of the increase in RHR observed with GLP-1 RA therapy ($P = 0.09$; Fig. 4*A*). No association was found between physical activity and HRV changes ($P = 0.66$; Fig. 4*B*). In addition, changes in physical activity were not associated with changes in 12-wk body weight ($P = 0.35$).

In the model for sleep duration, no significant group × time interaction or main effects of group or time were observed (Ps ≥ 0.11; Fig. 3*B*). Median split of the GLP-1 group by average minutes of sleep (422 min/night) suggested a trend whereby shorter nightly sleep duration was associated with a smaller increase in RHR ($P = 0.08$; data not shown). No association was found between sleep duration and HRV changes ($P = 0.55$; data not shown). Exploratory analysis

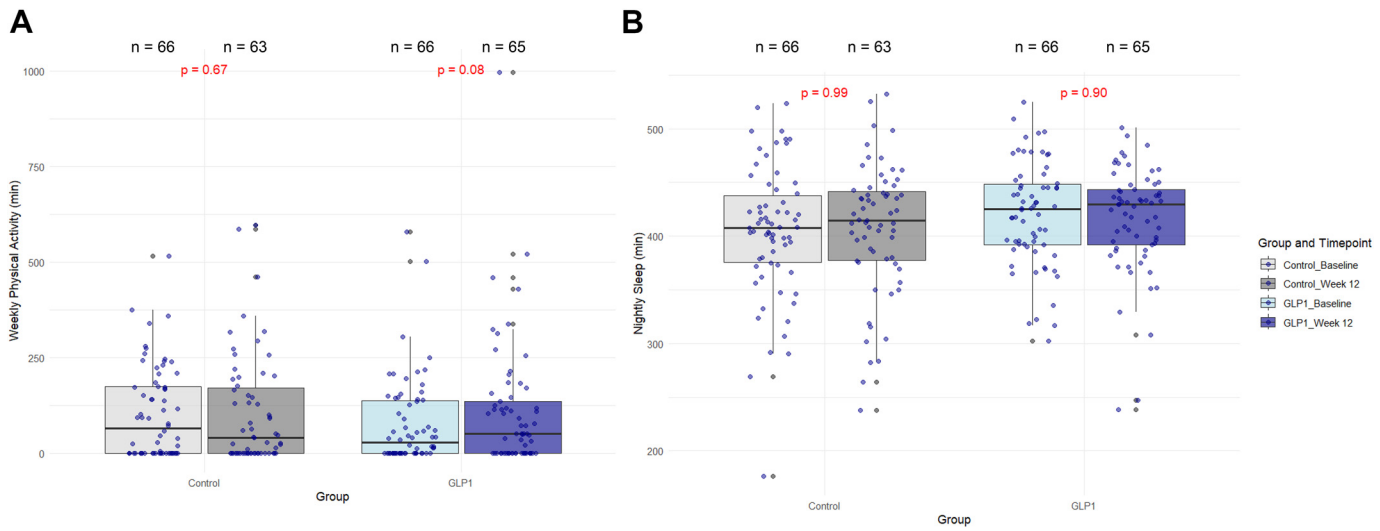


Figure 3. Weekly physical activity (*A*) and minutes of sleep (*B*) in glucagon-like peptide-1 (GLP-1) and Control groups. Boxplots display data for each group at baseline and *week 12*. Individual data points are overlaid to show within-group variability. The sample size at each time point is shown above the plots. The *P* values above come from post hoc within-group hypothesis testing between time points.

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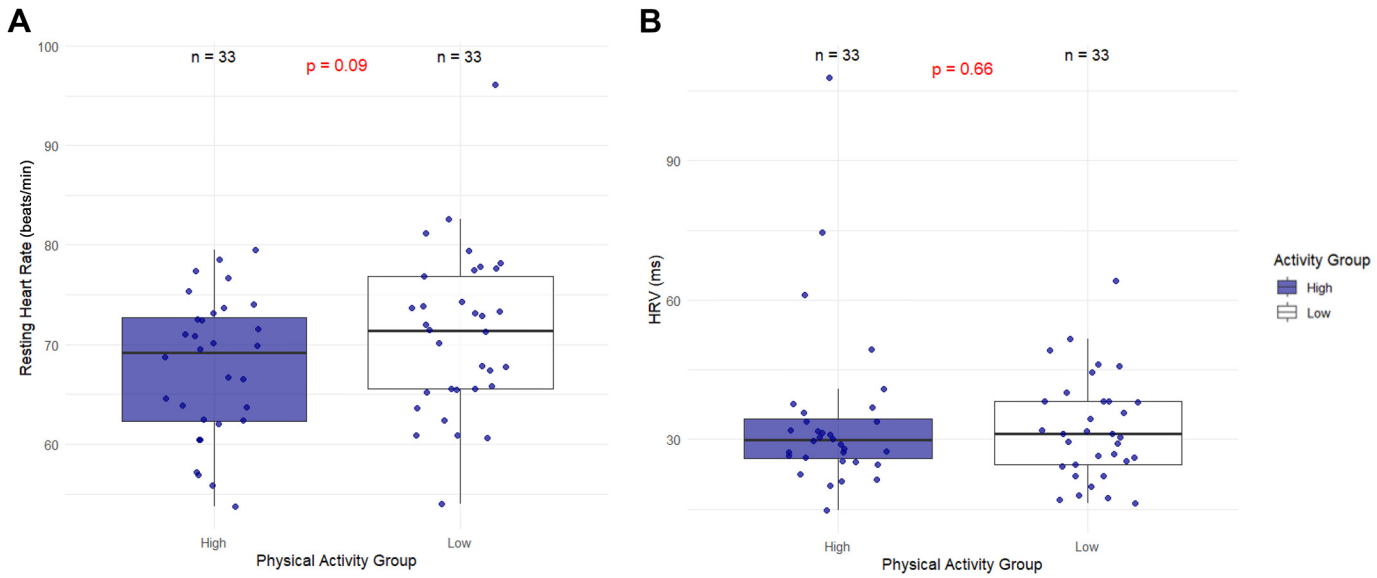


Figure 4. Comparison of resting heart rate (RHR; *A*) and heart rate variability (HRV; *B*) in high and low physical activity groups, derived using a median split of average daily physical activity. Boxplots show the distribution of data in each group, with individual participant data displayed as dots to show variability within each group. The sample size at each time point is shown above the plots. The *P* values above come from models fitting *week 12* cardiovascular values as the outcome, group as the input, and adjusting for baseline cardiovascular values.

examined interactions between sleep consistency, characterized as regularity of sleep onset and offset times over a 4-day window (12), with GLP-1 mediation and associated cardiovascular responses. No significant group × time interaction or main effects of group or time were observed (*P*s ≥ 0.47). In addition, sleep consistency was not associated with HRV or RHR changes (*P*s ≥ 0.71).

DISCUSSION

We leveraged longitudinal measurements, wearable technology, and causal inference to characterize cardiovascular and behavioral responses during the initial 12 wk of GLP-1 RA therapy. As hypothesized, GLP-1 RA therapy was associated with substantial weight loss, alongside significant increases in RHR mediated by reductions in HRV. Trends alluded to an increase in physical activity with GLP-1 RAs, which may play a role in attenuating the observed increase in RHR.

The observed ∼10% reduction in total body weight after only 12 wk of GLP-1 RA therapy in our real-world study matches, if not exceeds, the weight loss reported in large clinical trials of the latest GLP-1 RAs (i.e., ∼6%–9%) (1, 2). In addition, the proportion of our participants reporting a weight loss of ≥5% (i.e., 90%)—a clinically meaningful threshold (13)—after just 12 wk was comparable with what was achieved in these clinical trials after 12–18 mo (1, 2). These data underscore the profound weight loss efficacy of GLP-1 RAs in an everyday setting, with effects that appear amplified in our sample. The reasons behind this augmented weight loss are unclear; however, it is notable that Food and Drug Administration guidelines recommend that GLP-1 RAs be used alongside diet and exercise. Greater motivation, potentially associated with participants' willingness to invest in a wearable technology subscription, may contribute to improved medication adherence and behavior modification (i.e., diet and exercise) that promotes enhanced weight loss. However, it is also possible that wearable technology itself may play a role in facilitating behavior change that supports GLP-1 RA weight loss. Notably, changes in physical activity during the study period were not associated with changes in body weight, as may have been anticipated based on literature questioning the sufficiency of exercise alone for weight loss (14).

The cardiovascular changes observed in this study, specifically the increase in RHR and decrease in HRV following GLP-1 RA initiation, are consistent with the documented chronotropic (4) and autonomic (6) effects of GLP-1 RAs. However, the mechanism(s) by which GLP-1 RAs increase RHR remains a topic of debate. A recently published study used in vivo and ex vivo methods to demonstrate a direct chronotropic effect of GLP-1 on the heart that is mediated by GLP-1 receptors in pacemaker cells of the sinus node (4). In addition, a systematic review and meta-analysis on the effects of GLP-1 RAs on autonomic function in participants with diabetes concluded that increases in RHR with GLP-1 RAs seem to occur without an alteration of sympatho-vagal balance (i.e., autonomic function) (15). However, as the included studies exclusively involved chronic GLP-1 RA users, the possibility remains that the autonomic alterations seen with GLP-1 RAs, such as the decrease in HRV observed in the present study, may be short-lived. Interestingly, RR remained unchanged in our study, contrary to our hypothesis that it might decrease due to reductions in body mass (7). Longer observation periods are needed for a more comprehensive understanding of associations between RR and GLP-1 RA use. Nonetheless, it is noteworthy that our mediation analysis showed that HRV changes accounted for nearly three-quarters of the total effect of GLP-1 RAs on RHR, alluding to the autonomic nervous system's significant contribution to initial heart rate responses to GLP-1 RA medication. This finding aligns with prior evidence of autonomic

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involvement in RHR increases following acute GLP-1 RA administration in patients with type 2 diabetes (T2D) (16). Collectively, these findings indicate that the acute effects of GLP-1 RA therapy on RHR are likely at least partially mediated by alterations in autonomic function. The duration of this autonomic impact and its role in sustaining longer-term RHR increases observed in other studies (17, 18) is unclear, but worthy of future investigation.

Considering interactions between GLP-1 and dopamine signaling (19), it has been hypothesized that these medications may facilitate adoption and adherence to positive lifestyle changes, such as physical activity (20). Moreover, initial weight loss among individuals with overweight and obesity who begin GLP-1 RAs may alleviate discomfort associated with physical activity, thereby increasing the likelihood of exercise adoption and persistence. Consistent with this premise, trends in our study suggested an increase in physical activity among GLP-1 RA users, though statistical significance was not achieved. Similarly, a tendency toward attenuation of the RHR increase among GLP-1 RA users with higher versus lower levels of physical activity was observed. Although this result failed to meet the conventional significance threshold, the potential for even a modest level of physical activity (i.e., median split was at <10 min/day) to temper increases in RHR warrants consideration. Indeed, higher resting heart rate is a well-established independent risk factor for all-cause and cardiovascular mortality (21). Moreover, exercise participation is known to temper increases in RHR with advancing aging (22), providing evidence for the efficacy of physical activity to attenuate undesirable increases in RHR, albeit in a different context. Notably, post hoc sample size analysis for analysis of covariance with two predictors (baseline RHR and physical activity group) indicates that a total sample of 163 participants would be required to detect a statistically significant effect of the physical activity group on RHR, assuming a small-to-medium effect size observed in the current study ($f = 0.22$) with 80% power and an $\alpha = 0.05$. In sum, our real-world data suggest that a portion of individuals beginning GLP-1 RAs seem to increase physical activity participation, and, in doing so, may offset the RHR elevations associated with this medication.

Our findings should be interpreted in the context of our study's strengths and limitations. First, the study population was a convenience sample, which may have limited statistical power for certain analyses, such as those examining associations between GLP-1 RAs and behavior modification. Relatedly, though our sample consisted of a relatively balanced proportion of males and females (~60% male and ~40% female), we were unable to account for the potential influence of biological and sociocultural factors that may influence physiological and behavioral responses (23). Second, although participants self-reported GLP-1 RA use, we lacked specific detail on medication type (e.g., semaglutide and tirzepatide) and dosing strategies. Outside of overweight and obesity, GLP-1 RA medications are also prescribed for T2D and even off-label for cosmetic weight loss (24), but we lack a detailed medical history of our sample. Third, although participants wore the device almost daily and weekday versus weekend wear time was relatively similar between groups, our study design did not account for potential differences in cardiovascular metrics and health behaviors between weekdays and weekends (25). Last, body weight was self-reported among GLP-1 users and unavailable in our comparative group. In addition, over a third of participants in the GLP-1 group did not report their weight at *week 12*, possibly biasing our analysis. Objectively measured body weight and composition values in both cohorts would have enhanced our analysis. Furthermore, while we performed mediation analysis using HRV as a mediator and RHR as an outcome, we could not account for their bidirectional influence, limiting causal inference. Notable strengths of this study include our use of propensity matching for causal inference on real-world data, being among the first to report serial (i.e., daily) measurements of cardiovascular measures and health behaviors among GLP-1 RA users, and our use of wearable technology that has been validated against gold-standard electrocardiogram and polysomnography measures with a low degree of bias and low precision of errors (10, 11).

In conclusion, we demonstrate substantial weight loss and significant increases in RHR mediated by reductions in HRV during the initial 12 wk of GLP-1 RA therapy. In addition, we observed trends portending to an increase in physical activity with GLP-1 therapy in conjunction with evidence that physical activity may help to temper GLP-1-associated RHR increases. These findings are among the first to provide daily insights into cardiovascular and behavioral responses following GLP-1 initiation, offering valuable data for understanding the real-world impact of this medication.

DATA AVAILABILITY

The data that support the findings of this study are not publicly available due to intellectual property concerns of WHOOP, Inc. Data may be made available upon request to the company via research@whoop.com for researchers who meet the criteria for access to confidential data.

DISCLOSURES

G.J.G. is an employee of Medifast Inc. and a past employee of WHOOP. J.K., F.F., S.R.J., W.v.H., C.C., and K.E.H. are employees of WHOOP. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

G.J.G. conceived and designed research; G.J.G. performed experiments; G.J.G., W.v.H., and J.K. analyzed data; G.J.G. and W.v.H. interpreted results of experiments; G.J.G. prepared figures; G.J.G. drafted manuscript; G.J.G., J.K., F.F., S.R.J., C.C., W.v.H., and K.E.H. edited and revised manuscript; G.J.G., J.K., F.F., S.R.J., C.C., W.v.H., and K.E.H. approved final version of manuscript.

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