Title: Assessment of a Decision Support System for Adults with Type 1 Diabetes on Multiple Daily Insulin Injections

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Short title: Assessment of a Decision Support System

Key words: type 1 diabetes, decision support, continuous glucose monitoring, exercise, hypoglycemia

Introduction: DailyDose is a decision support system designed to provide real time dosing advice and weekly insulin dose adjustments for adults living with type 1 diabetes using multiple daily insulin injections.

Materials and Methods: Twenty-five adults were enrolled in this single-arm study. All participants used Dexcom G6 for continuous glucose monitoring, InPen for short-acting insulin doses, and Clipsulin to track long-acting insulin doses. Participants used DailyDose on an iPhone for 8 weeks. The primary endpoint was % time in range (TIR) comparing the 2-week baseline to the final 2-week period of DailyDose use.

Results: There were no significant differences between TIR or other glycemic metrics between the baseline period compared to final 2-week period of DailyDose use. TIR significantly improved by 6.3% when more than half of recommendations were accepted and followed as compared with 50% or less of recommendations (95% C.I. 2.5-10.1%, P=.001).

Conclusions: Use of DailyDose did not improve glycemic outcomes as compared to the baseline period. In a post hoc analysis, accepting and following recommendations from DailyDose was associated with improved TIR.

Clinical Trial Registration number: NCT04428645

Introduction

Hyperglycemia and hypoglycemia are commonplace for people living with type 1 diabetes (T1D). Continuous glucose monitoring (CGM) has significantly reduced, but not eliminated, dysglycemia.[1] Automated insulin delivery can further reduce dysglycemia,[2-4] but requires the use of an insulin pump and is inaccessible for some. Many people living with T1D continue to use multiple daily insulin (MDI) injections.[5] DailyDose is an iPhone application that is designed to support this population by 1) allowing for bolus calculation based on inputs including carbohydrate intake, CGM value and trend, and exercise information, 2) providing recommendations for carbohydrate intake based on exercise type, intensity, and duration, and 3) providing weekly recommendations for adjustments in insulin doses at specific times of day, including basal insulin dose, carbohydrate ratios or fixed mealtime doses, and correction factor.[6] An example screen from DailyDose is shown in Figure 1. Described here are results from the first proof of concept study evaluating glycemic outcomes with use of DailyDose over 8 weeks as compared to 2 weeks of use of CGM alone.

Methods

From July 2020 to November 2021, 25 adults with T1D were enrolled at Oregon Health & Science University. Participants provided written informed consent. This study was conducted under U.S. Food and Drug Administration–approved investigational device exemption and OHSU Institutional Review Board approval.

The inclusion criteria required diagnosis of T1D for at least 1 year, ages 18 to 60 years, use of MDI, and A1C of 7.0-10%. Exclusion criteria included pregnancy or intending to become

pregnant, cardiovascular disease, estimated glomerular filtration rate <60 mL/min, hypoglycemia unawareness, or an episode of severe hypoglycemia in the past 6 months. For the 2-week baseline period, participants wore Dexcom G6 and continued their typical insulin doses. CGM alarms were set at 70 mg/dL and 250 mg/dL for both baseline and intervention periods. After completion of the baseline period, participants were provided with a smartphone running DailyDose. For short-acting insulin, participants were provided InPen devices (Companion) with Novolog cartridges (Novo Nordisk). Insulin doses were relayed via Bluetooth and captured in HealthKit (Apple), which relayed these data to DailyDose for calculation of insulin-on-board. Long-acting insulin doses were captured using Clipsulin and the DIABNEXT app (DIABNEXT). DailyDose displayed CGM and allowed for short-acting insulin dose calculation based on CGM values and trends or capillary blood glucose values, insulin-on-board, carbohydrate input, carbohydrate ratio(s), correction factor(s), and target(s). DailyDose also incorporated advice for managing glucose with exercise based on a published consensus statement[7] with recommendations to reduce short-acting insulin doses or ingest additional carbohydrate. DailyDose used machine learning forecasting algorithms to alert the participant when glucose was predicted to be low within the next 30 minutes[8] and also in the event of predicted nocturnal hypoglycemia.[9] DailyDose provided up to five recommendations each week using a case-based reasoning algorithm.[6] Weekly recommendations could include adjusting basal insulin dose, carbohydrate ratios, or correction factors specific to certain times of day. To reflect real world use, participants could accept or reject each individual recommendation without input from the study team. *Accepting* a recommendation means that if the app recommended a change to insulin dosing (e.g. change a carbohydrate ratio or correction factor at a certain time of day), then the participant accepted that change and the setting was changed in the app. We also

considered whether the person *followed* the recommendations. A person *followed* the recommendations if they dosed insulin within ±25% of what was recommended by the DailyDose bolus calculator and if they used the bolus calculator for at least 75% of short-acting insulin boluses recorded by the InPen. Due to the long-acting properties of degludec and glargine U-300, participants using these insulins were only given recommendations to adjust long-acting insulin at most every 2 weeks. A study investigator set constraints on maximum/minimum settings for short- and long-acting insulin during the onboarding process. DailyDose was not able to recommend insulin dose changes outside of this range.

The prespecified primary outcome was % TIR (CGM 70-180 mg/dL) comparing the final 2-week period of use of DailyDose with the 2-week baseline period. Secondary endpoints based on CGM values were mean glucose, % time <70 mg/dL, % time <54 mg/dL, % time >180 mg/dL and % time >250 mg/dL. We estimated that 20 subjects provide 90% power to detect a paired difference in % TIR of 10% or more on the absolute scale between the first and final 14 days of the study, assuming a standard deviation (SD) of 13% and a two-sided test with alpha = 0.05. Differences were evaluated longitudinally using generalized linear mixed effects models with an indicator variable for final vs. baseline period and a random intercept for participant. We use linear regression for mean glucose and beta regression[10] for % time in the defined glucose ranges. We report p-values from the Wald test of time period. For two skewed variables, % time <54 mg/dL and the coefficient of variation of glucose, we used the nonparametric Wilcoxon matched-pairs signed-rank test. Additionally, for the primary outcome, we examined potential effects of enrollment sequence as well as % of missing CGM data.

An added post hoc analysis assessed the impact of accepting and following recommendations on glycemic outcomes. Specifically, we compared glucose outcomes on weeks when more than

50% of recommendations were *accepted* and *followed* on the prior week as compared to when less than 50% of recommendations were *accepted* and *followed* on the prior week. For most weeks, 100% of recommendations were either *accepted* and *followed* (n=65) or 100% of recommendations were rejected or not followed (n=27). For a smaller number of weeks, a subset of recommendations were accepted while other recommendations were rejected (n=14). We chose a cut-off of 50% for *accepted* and *followed* recommendations post-hoc to determine if generally accepting and following recommendations leads to better glucose outcomes compared with not accepting and following recommendations. However, we found that improvement in TIR improved linearly for the case when no recommendations were *accepted* and *followed* (0% of recommendations *accepted* and *followed*), to some recommendations *accepted* and *followed* (>0 and < 100%), to all recommendations *accepted* and *followed* (100%) as shown in Supplementary Figure 1. Starting after the baseline run-in, CGM data were aggregated into 7-day periods. TIR was centered on each participant's mean and was modeled as a function of having *accepted* and *followed* the previous week's recommendations, controlling for week and for baseline TIR. The mixed effects model included a random intercept for participant and an autoregressive structure on the residuals to account for the correlation between observations from the same person and adjacent in time.

Analyses were conducted using Stata version 16.1 and SAS version 9.4 for Windows (SAS Institute, Cary NC) using the GLIMMIX procedure for beta regression.

Results

Twenty-five adults living with type 1 diabetes were enrolled, consisting of 1 Asian, 2 Black, and 22 White participants with a mean age of 35.8 years. Fourteen of the participants were female.

Participants had a baseline A1C 8.2% and 60% used CGM prior to study enrollment. One participant withdrew due to CGM connectivity issues and was not included in the analysis.

TIR was not significantly different during the baseline 2-week period as compared to the final 2-week period of DailyDose use (mean ± SD of 50.7 ± 14.9% versus 46.9 ± 17.8%, P = 0.25). There was no significant difference in improvement in TIR for those who used CGM prior to the study as compared to those who did not (P=.186). Similarly, secondary endpoints of mean glucose, % time <70 mg/dL, and other glycemic metrics were not significantly different between the two periods (Table 1). TIR significantly improved by 6.3% in a post hoc analysis when comparing weeks when more than half of recommendations were accepted and followed within a week, as compared to half or less of recommendations (95% CI 2.5-10.1%, P=.001, Figure 2). The weekly % of recommendations that were accepted had a bimodal distribution. All of the recommendations were accepted for 62% of the study weeks, none were accepted for 25% of the weeks, and some of the recommendations were accepted for 13% of the weeks.

A total of 6,694 short-acting insulin doses were recorded during the study (range 54-651 across participants). The DailyDose bolus calculator was used for 81.9% of short-acting insulin doses. When the bolus calculator was used, 67.5% of the time the dose delivered was within 0.5 units of the dose recommended by DailyDose, 14.7% of the time the dose delivered was more than 0.5 units above the recommended dose, and 17.8% of the time the dose delivered was more than 0.5 units below the recommended dose. Post hoc, we evaluated whether TIR was associated with the percent of the time in a week when participants followed the short-acting insulin DailyDose bolus calculator recommendations within ±0.5 units using a mixed effects model while controlling for (1) the percent of time that the user accepted the weekly recommendations that week, and (2) the percent of the time that the bolus calculator was used when short-acting insulin

was dosed. This mixed effects analysis showed that compared with a baseline when the bolus calculator would never be used to deliver insulin within ±0.5 units, there was a 16.9% increase in TIR for weeks when participants would consistently deliver insulin within this ±0.5 units range (P=.012). Importantly, there was no increased likelihood of hypoglycemia associated with following the DailyDose bolus calculator within ±0.5 units (P=.159).

There were no serious adverse events.

Discussion

Improving glucose control in people living with T1D on MDI with the use of decision support is challenging. There have been numerous published approaches to decision support for management of type 1 diabetes.[11] In a multi-center randomized controlled trial involving adults and adolescents living with T1D,[12] TIR improved similarly with respect to baseline in both groups with no significant difference with decision support, but outcomes improved for active users of the decision support app. In the current study, TIR did not improve during the final 2-week period with the use of DailyDose as compared to the baseline 2-week period. Accepting and following more than half of DailyDose recommendations within a week was associated with improved TIR. The direction of causality is not clear. This improvement could have been related to the impact of the recommendations or the behavior of accepting recommendations may be associated with other behaviors such as better adherence to their diabetes regimen. An increase in percent TIR of 16.9% was associated with delivery of short-acting insulin as recommended by the DailyDose bolus calculator within ±0.5 units. This is not surprising, as we would expect that following the bolus calculator guidelines would result in less hypo- and hyperglycemia and improved TIR. The DailyDose bolus calculator is different than current commercial bolus

calculators in that it adjusts insulin dose recommendations based on not just the current CGM level and estimated carbohydrate intake, but also in response to the CGM trend and anticipated exercise (Figure 1, left panel). The association of a significant improvement in TIR when the bolus calculator was followed may be partially due to including CGM trend and anticipated exercise in the bolus calculation, however further study is required to confirm this.

Limitations of this study include small sample size and lack of a randomized control arm. In addition, 40% of participants did not use CGM prior to the study, which could have impacted glucose control over the course of the study as CGM is known to improve glycemic control in adults with type 1 diabetes on MDI.[1] However, all participants used unblinded CGM during the baseline 2-week period given this known beneficial impact of CGM and there was no difference in change in TIR between pre-study CGM users and non-CGM users.

For many, decision support alone may not be sufficient to improve glycemic control as it does not address issues such as taking insulin after eating or missed insulin doses. Diabetes self-management education and support (DSMES) is a key aspect of diabetes care and is important for addressing issues such as mistimed insulin doses.[13] Timing of insulin administrations and rates of missed insulin doses were not collected as a part of this study and may have been important contributors to hyperglycemia. Participants used the DailyDose bolus calculator and took the recommended dose approximately 55% of the time. It is important for bolus calculators to be simple, fast and easy to use. And they should enable users to quickly understand the scenarios under which it is best to override the bolus calculator. In addition, diabetes distress may significantly impair self-care and impact quality of life and may require behavioral health intervention.[14] Behavioral health services and DSMES were not components of the study described here. It is feasible that combining decision support with other interventions such as

diabetes education and/or behavioral health services may lead to better outcomes and this is a potential area for future research.

Conclusion

Use of DailyDose did not improve glycemic outcomes as compared to the baseline period. In a post hoc analysis, accepting and following recommendations from DailyDose was associated with improved TIR. Future research is needed to increase explainability and transparency of decision support systems to enable increased acceptance of recommendations. Further work is also needed to assess if incorporating additional interventions such as DSMES alongside decision support can improve TIR and quality of life.

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Author Contributions. JRC, PGJ, LMW, and JEY contributed to the writing, literature search, study design, data collection, data interpretation, and decision support system construction. PGJ, NST, GMY, JRC, LMW, JEY, CML, JP, SMO, WWH, RHD, JAC, and KWS contributed to decision support system construction. DLB, VBG, and JHE contributed to the data collection. KR, AZE, PGJ, and TK contributed to the statistical analysis.

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Table 1: Comparisons of CGM metrics for 2-week baseline period and final 2-week DailyDose period. P value for the difference baseline and final periods for n=24 study participants using (a) mixed effects beta regression for % TIR, (b) mixed effects linear regression for mean glucose, or (c) nonparametric Wilcoxon matched-pairs signed-rank test for highly skewed percent time <54 mg/dL and glucose coefficient of variation. Data are aggregated to one observation per person per period for analysis.

	Baseline 2-week period		Final 2-week DailyDose period		Difference		
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**p**
Primary endpoint							
Time spent 70-180 mg/dL, %	50.7	(14.9)	46.9	(17.8)	-3.8	(15.8)	0.25[a]
Secondary endpoints							
Mean glucose, mg/dL	184	(24)	194	(33)	11	(28)	0.057[b]
Time spent <70 mg/dL, %	1.6	(1.6)	1.3	(1.3)	-0.3	(1.0)	0.180[a]
Time spent <54 mg/dL, %	0.183	(0.385)	0.184	(0.383)	0.0006	(0.472)	0.46[c]
Time spent >180 mg/dL, %	47.7	(15.5)	51.8	(18.0)	4.1	(15.9)	0.224[a]
Time spent >250 mg/dL, %	16.9	(10.1)	22.3	(16.4)	5.4	(12.5)	0.025[a]
Coefficient of variation, %	34.7	(4.5)	34.4	(4.1)	-0.3	(4.2)	0.67[c]

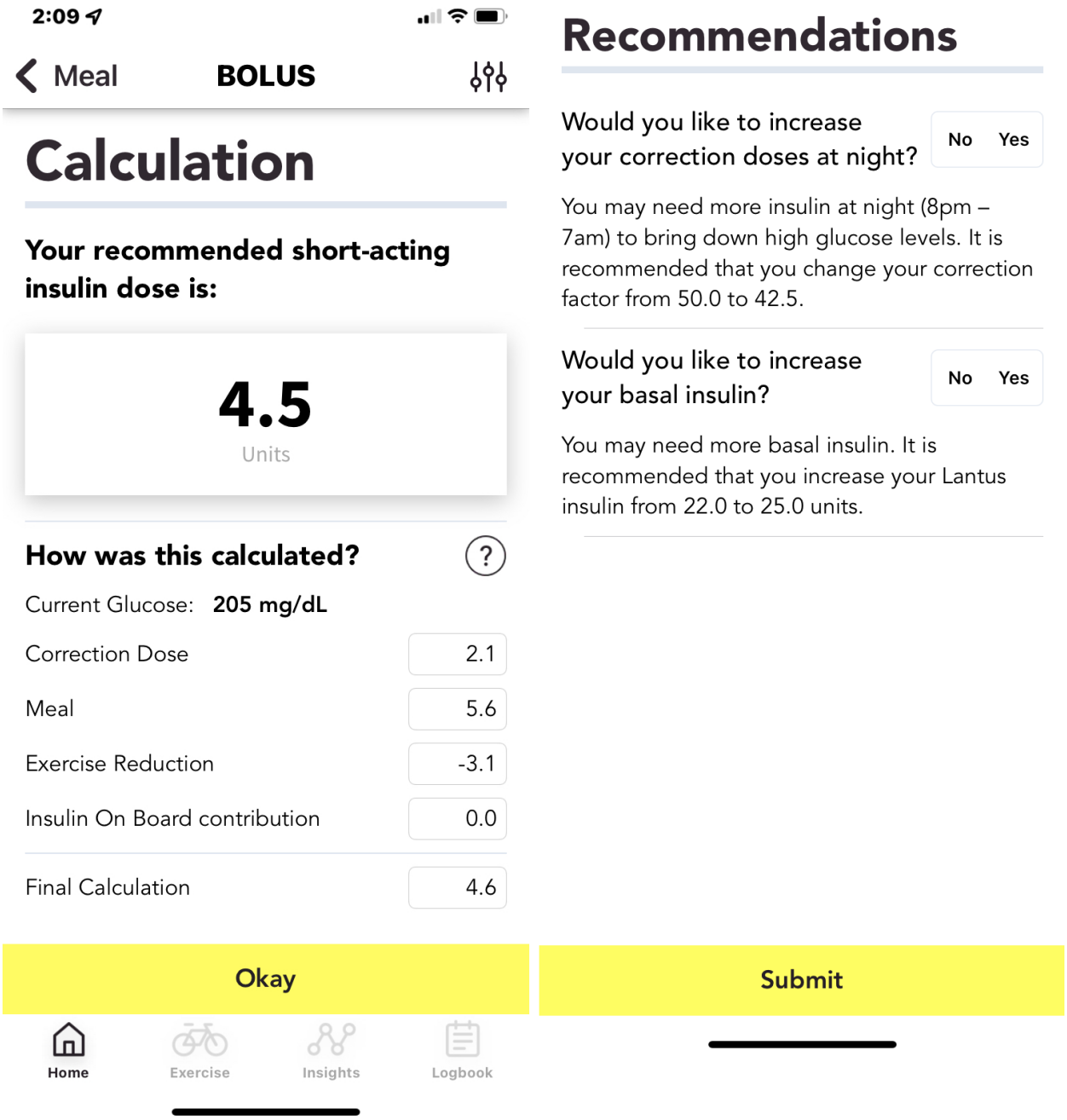


Figure 1: Example screenshots from DailyDose. The left panel shows the bolus calculator screen indicating the recommended short-acting insulin dose calculated based on a glucose of 205 mg/dL and estimated meal carbohydrates, with a reduction in the insulin dose for planned exercise. The right panel shows two example recommendations, one recommending a change in the correction factor and one recommending a change in basal insulin dose.

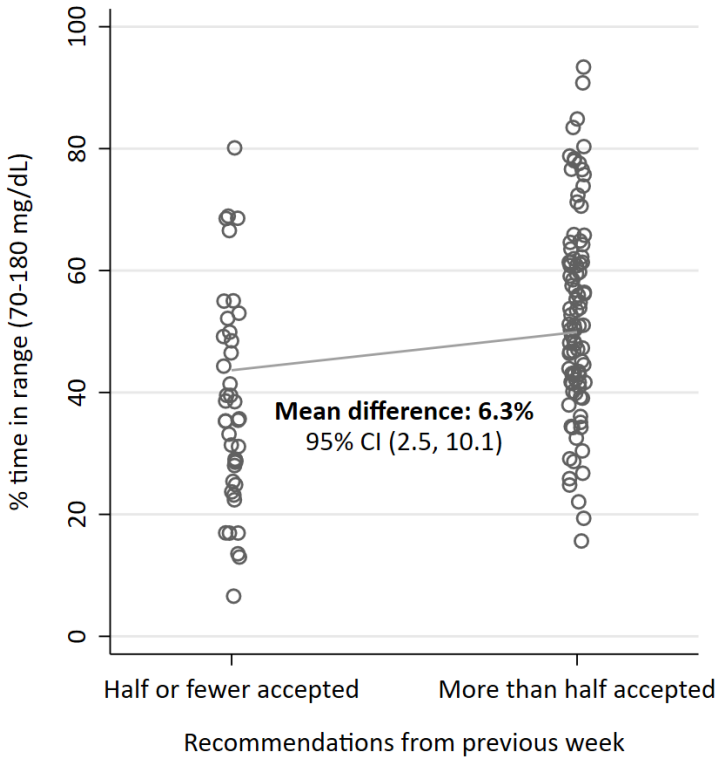
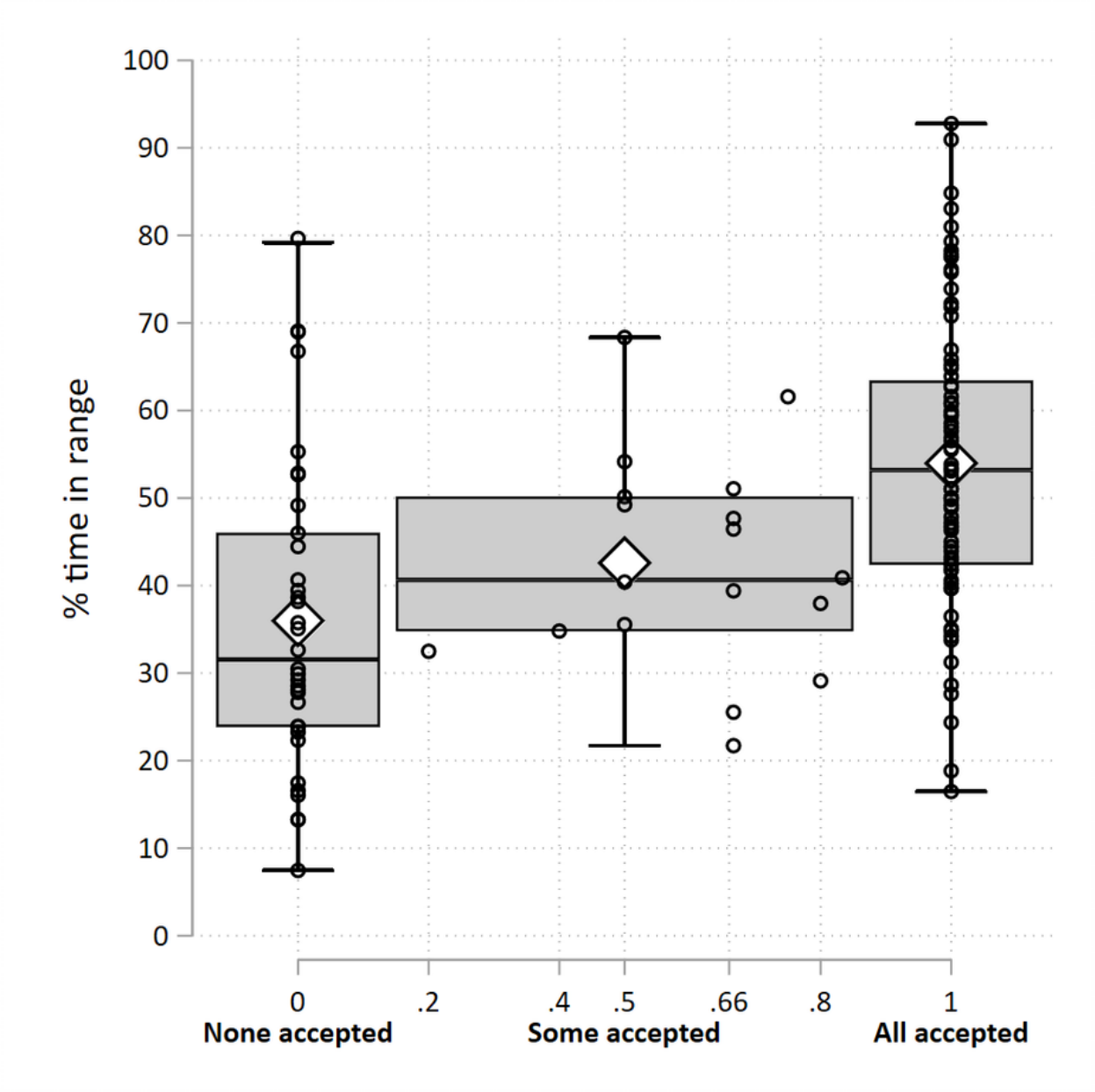


Figure 2: Plot of % TIR comparing weeks during which half or fewer recommendations were accepted during the prior week as compared to when more than half of recommendations were accepted. N = 24 participants and 184 weeks. Note that TIR increased by a mean of 6.3% (P = .001) when more than half of recommendations were accepted and followed, as compared to when less than half of recommendations were accepted. Mean difference estimated using a longitudinal mixed effects regression model controlling for percent time in range at baseline, week of observation, and adherence.



Supplementary Figure 1: Plot of % time in range comparing weeks during which none of the recommendations were accepted and followed during the prior week as compared to when some of recommendations were accepted and followed (>0% and <100%) as compared to when all of the recommendations were accepted and followed. N = 24 participants and 184 weeks. Note that time in range increased linearly across the three groups.