A randomized clinical trial comparing low-fat with precision nutrition–based diets for weight loss

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A randomized clinical trial comparing low-fat versus precision nutrition-based diets for weight loss: impact on glycemic variability and HbA1c

Short running title: Precision nutrition and glycemic outcomes

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List of Abbreviations:

CONGA	continuous overall net glycemic action
CGM	continuous glucose monitor
CV	coefficient of variation
eGFR	estimated glomerular filtration rate
GV	glycemic variability
MAGE	mean amplitude of glycemic excursions
NYULH	New York University Langone Health
PNP app	Personalized Nutrition Project mobile application
PPGR	postprandial glucose response
SD	standard deviation
T2D	type 2 diabetes

Protocol and data access: Study protocol and deidentified data will be shared upon request via email to Dr. Lauren Berube at lauren.thomas@nyulangone.org.

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Abstract (300-word limit, current: 284 words):

Background: Recent studies have demonstrated considerable inter-individual variability in postprandial glucose response (PPGR) to the same foods (1), suggesting the need for more precise methods for predicting and controlling PPGR. In the Personal Nutrition Project, the investigators tested a precision nutrition algorithm for predicting an individual's PPGR.

Objective: To compare changes in glycemic variability (GV) and HbA1c in two calorie-restricted weight loss diets in adults with prediabetes or moderately-controlled type 2 diabetes (T2D), which were tertiary outcomes of the Personal Diet Study.

Research Design: The Personal Diet Study was a randomized clinical trial to compare a one-size-fits-all low-fat diet (hereafter, *Standardized*) versus a personalized diet (hereafter, *Personalized*). Both groups received behavioral weight loss counseling and were instructed to self-monitor diets using a smartphone app. *Personalized* received personalized feedback via the app to reduce their PPGR. Continuous glucose monitoring (CGM) data were collected at baseline, 3- and 6-months. Changes in mean amplitude of glycemic excursions (MAGE) and HbA1c at 6 months were assessed. We performed intention-to-treat analysis using linear mixed regressions.

Results: We included 156 participants (66.5% female, 55.7% White, 24.1% Black, mean age 59.1 years (SD=10.7)) in these analyses (*Standardized* = 75, *Personalized* = 81). MAGE decreased by 0.83 mg/dL per month for *Standardized* (95% CI: 0.21, 1.46 mg/dL; p = 0.009),

and 0.79 mg/dL per month for *Personalized* (95% CI: 0.19, 1.39 mg/dL; p = 0.010), with no between group differences (p = 0.92). Trends were similar for HbA1c.

Conclusions: *Personalized* diet did not result in a greater reduction in GV or HbA1c in patients with prediabetes and moderately-controlled T2D, compared to a *Standardized* diet. Additional subgroup analyses may help to identify patients who are more likely to benefit from this personalized intervention.

Key Words: precision nutrition, diabetes, personalized nutrition, glycemic variability, MAGE, low fat diet

Background

Elevated postprandial glucose response (PPGR) increases oxidative damage (2) and has been found to be an independent risk factor for the development of obesity (3), liver disease (4, 5), type 2 diabetes (T2D), cancer (6), and cardiovascular disease (7, 8), as well as mortality from all causes (9, 10), cardiovascular disease (7), and cancer (11).

Conventional dietary strategies for minimizing PPGR are based on limiting the glycemic load of meals and snacks by moderating the intake of carbohydrates with low-carbohydrate or ketogenic diets and promoting whole plant foods that contain soluble dietary fiber. However, clinical trials exploring the efficacy of low-carbohydrate and low-glycemic load diets have been mixed and mostly negative (12-18), perhaps because they used one-size-fits-all dietary approaches. Recent studies have demonstrated considerable inter-individual variability in PPGR to the same foods (1), suggesting the need for more precise methods for predicting and controlling PPGR.

In the Personal Nutrition Project (hereafter, PNP), the co-principal investigator (ES) devised the first personalized machine learning algorithm for predicting an individual's PPGR. In brief, a training data set was compiled from 800 individuals that included a pool of over 70 features including profiling using metagenome sequencing to capture key gut microbiota-based features associated with glucose tolerance and glycemic responses (e.g., bacterial abundances, bacterial diversity, bacterial growth rates, gene abundances, biologic pathway abundances, Single Nuclei Polymorphisms and structural variations). Also collected were one full week of interstitial glucose measurements using a continuous glucose monitor (CGM), a one-week log of date- and time-stamped meals and snacks with related nutritional information (e.g., macronutrient distribution), HbA1c, and participant characteristics (e.g., physical activity, sleep

times, stress and hunger levels recorded in a PNP mobile app). Using stochastic gradient boosting regression methods, data were extracted from the training set in an iterative fashion that allowed the computer to "learn" from prior data and build an optimized model for predicting PPGR. The derived model was validated in a new cohort of 100 participants, with the algorithm dramatically outperforming carbohydrate content in predicting glycemic response (19). The algorithm was validated in a US sample (20). Details regarding this algorithm have been published elsewhere (1, 19, 20).

The Personal Diet Study was a randomized clinical trial to compare two weight loss interventions, a one-size-fits-all low-fat diet (hereafter, *Standardized*) versus a diet guided by the PNP algorithm (hereafter, *Personalized*). As we presented in a prior publication, no statistically significant between groups differences in weight loss were observed (21). The purpose of the current report is to examine between group differences in glycemic variability (GV) and HbA1c during the active intervention period. We hypothesized that compared to those randomized to *Standardized*, individuals randomized to *Personalized* would have greater reductions in GV and HbA1c at 6 months.

Methods

Study objective and approvals

The Personal Diet Study was a randomized controlled trial to compare the effects of *Personalized* and *Standardized* diet interventions on weight loss in participants with prediabetes or moderately-controlled T2D (ClinicalTrials.gov Identifier: NCT03336411). The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the NYU Grossman School of Medicine Institutional Review Board (IRB #17-00741). Informed consent was obtained from all study participants. A detailed study design and

intervention protocol have been published elsewhere and are briefly described here (22, 23). The goal of this report is to examine between group differences in GV and HbA1c at 3 months and 6 months follow-up.

Participants

Participants were recruited primarily from NYU Langone Health (NYULH) between January 2018 and March 2021. Potentially eligible participants received an IRB approved message on their MyChart patient portals, where a brief overview of the study and an invitation to self-refer were provided. Participants were also recruited from ClinicalTrials.gov and iConnect, which is a NYULH hosted website outlining all the active clinical trials conducted at NYULH and can serve as a platform for self-referral. English speaking adults ages 18 to 80 years old, with comorbid overweight or obesity (27 $kg/m^2 \leq$ body mass index (BMI) ≤ 50 kg/m^2) and prediabetes or moderately-controlled T2D ($5.7\% \leq$ HbA1C $\leq 8\%$) managed with lifestyle alone or lifestyle plus metformin, with an estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73 m^2, were eligible for the study. See **Supplementary Table 1** for detailed eligibility criteria.

Screening and Data Collection Procedures

Pre-screening to determine potential eligibility and interest was conducted via phone. Before the COVID-19 pandemic, potential participants were scheduled for an in-person visit at the Clinical Research Center at the NYULH Clinical and Translational Science Institute (CRC-CTSI), to obtain consent and additional screening measurements (HbA1c, eGFR). Initially, height was measured to the nearest 1 cm using a SECA 213 Stadiometer (Seca GmBH & Co.

KG, Hamburg, Germany), and weight measured to the nearest 0.1 kg in light clothing without shoes using a Stow-Weight scale (Scale-Tronix, Welch Allyn, Skaneateles, NY, USA).

Due to the COVID-19 pandemic, after March 15, 2020, in-person screening, consent, and measurement procedures were conducted via videoconferencing (Cisco Webex, San Jose, California, USA). Weight was obtained from an electronic scale shipped to potential participants (RENPHO, Joicom Corporation, Eastvale, CA, USA), and data were transferred via Bluetooth to a corresponding mobile application which study staff were able to access electronically. Height was self-reported. HbA1c and eGFR values were obtained from electronic medical records if performed within the last 6 months. Otherwise, potential participants were guided via Webex to obtain point-of-care HbA1c using the study-provided A1cNow monitor (PTS Diagnostics, Whitestown, IN, USA). Kidney disease diagnosis was used in lieu of eGFR data, if eGFR data were not available.

Randomization

Randomization was done in blocks of 4 to equally allocate participants to one of two arms: (1) *Standardized* or (2) *Personalized*. Each study ID was preassigned a randomization arm. As will be discussed in the Intervention Strategy below, blood testing and stool samples were required by the PNP algorithm for predicting PPGRs in *Personalized* participants. Additionally, stool samples were shipped to Israel for processing and programming of the PNP app to provide PPGR feedback that was personalized to the individual participant. Because of limited resources, and in order to minimize participant burden and delays in reprogramming of the PNP app, blood and stool samples were collected from *Personalized* participants at baseline. In other words, randomization was performed prior to baseline assessment. However, randomization was

performed by the study statistician, independent of measurements; the data reported here were derived from objective measures not subject to investigator bias, and participants remained blinded to randomization assignment until week 5 of the intervention.

Intervention Strategy

Both Groups. Participants in both groups received an intensive technology-supported behavioral intervention program targeting 7% weight loss and a calorie goal (deficit of 500 kcal/day). Originally, participants' calorie goals were calculated using resting energy expenditure, measured using indirect calorimetry (Quark RMR, COSMED; Rome, Italy) with an activity factor of 1.4. In March 2020, due to the COVID-19 pandemic, we discontinued the use of indirect calorimetry; and calculated participants' calorie goals using the Mifflin St-Jeor equation with an activity factor of 1.4 (24). Participants engaged in registered dietitian-led, group-based, behavioral counseling that was informed by Social Cognitive Theory (25) and the Diabetes Prevention Program (DPP) (26). Counseling was conducted via Webex weekly for 4 weeks, then every other week for 20 weeks. Sessions covered both educational content (e.g., obesity risks, benefits of weight loss, strategies for restricting calories, aerobic exercise and strength training, dealing with weight loss plateaus) and behavioral strategies (e.g., establishing relevance of behavior change, goal setting, self-reward, and problem solving around common barriers to weight loss success). To assure fidelity, each session was anchored by two brief (~5 minute) animated videos which were interspersed with open-ended questions designed to elicit discussion about experiences, values and feelings; evaluate learning; and provide participants with the opportunity to practice applying new content (e.g., evaluating dietary intake, setting goals, seeking solutions around barriers encountered). Each session lasted approximately one hour. Participants were advised to

149 gradually build to 150 minutes/week of moderate-to-vigorous physical activity. They were also
150 directed to self-monitor planned meals using the PNP mobile application for an approximately 5-
151 month period, starting from the first day of the intervention. The PNP app provided real-time
152 feedback regarding dietary intake in relation to the intervention targets specific to their
153 randomization assignment (see below). Participants were expected to enter their dietary intake data
154 for about 5 months.

155 For those who did not have a smartphone, a study phone was provided free of charge.
156 Summary reports were sent to participants via email every week for the first four weeks that
157 dietary self-monitoring was expected, and every other week for twenty weeks (22, 23). These
158 reports contained information about dietary self-monitoring adherence, weight loss trajectory,
159 calorie targets, and dietary targets (See **Supplementary Figure 1a and 1b**). Adherence to
160 physical activity recommendations was not accessed, and feedback about physical activity was
161 not provided to study participants.

162 *Standardized*. *Standardized* participants were advised to consume less than 25% of their
163 calories from total fat. The PNP mobile app provided real-time feedback regarding calorie intake
164 and macronutrient distribution of meals and snacks logged by participants.

165 *Personalized*. *Personalized* participants received the same PNP mobile app feedback as
166 the *Standardized* participants, plus meal scores reflecting their predicted PPGR derived from the
167 PNP algorithm (19). To generate meal scores, stool samples were collected in the *Personalized*
168 arm-only at baseline using an OMNIgene Gut stool collection kit (OMR-200; DNA Genotek
169 Inc., Ottawa, ON, Canada). Stool samples were shipped to the Weizmann Institute for
170 microbiome analysis. Features of the gut microbiome were combined with participant level data
171 (HbA1c, anthropometrics, sociodemographic and health variables) to generate personalized meal

scores, which were displayed by the PNP app when planned meals or snacks were logged into the app. Meal scores were color-coded using a traffic-light motif with green scores indicating an "excellent" or "very good" PPGR, yellow scores indicating a "good" PPGR, and red scores indicating a "bad" or "very bad" PPGR. Participants were trained to experiment with different food choices (e.g., smaller serving sizes, different ingredients, the addition of healthy fats) to improve their score while remaining under their calorie targets.

Outcomes Assessments

Glycemic variability and HbA1c measurements were collected at baseline, 3-, and 6-months.

Glycemic variability. The primary objective of this manuscript was to examine the differences in mean amplitude of glycemic excursions (MAGE) at 3 months and 6 months compared to baseline. Secondary endpoints included other measures of GV: mean of CGM glucose readings, standard deviation (SD), coefficient of variation (CV), and continuous overall net glycemic action (CONGA).

Participants wore the Abbott FreeStyle Libre Pro (Abbott Park, IL, USA) CGM, which measured interstitial glucose values every 15 minutes for up to 14 days. Participants were blinded to the CGM data. As per manufacturer's information, data collected in the first 12 hours of CGM placement may produce inaccurate readings related to calibration, therefore these data were removed from analysis (27). Every 24-hour period during which CGM failed to record at least 2 consecutive hours of glucose readings, was excluded from analysis, as this may result in unreliable MAGE estimates (28). After missing glucose values were interpolated, GV measures were calculated for every 24-hour period using EasyGV version 9.0.R2 (Nathan R. Hill, University of Oxford, United Kingdom) and averaged across CGM collection days for baseline,

3-months, and 6-month assessments. Participants with at least one day of CGM data were included in the analytic sample.

HbA1c. Initially, HbA1c values were obtained at each assessment time period at the CRC-CTSI via venipuncture and analyzed using high-pressure liquid chromatography (HPLC, Variant II) Turbo analyzer. After the start of the COVID-19 pandemic, HbA1c values were obtained from patients' electronic medical records, or using A1cNow monitors that were shipped to participants' homes at baseline only.

Adverse Event Monitoring

All potential adverse events reported by participants were assessed by the principal investigator and research physician, to determine severity and relatedness to study protocol. The IRB was informed of all reportable information. No severe adverse events were identified.

Statistical Analysis

Descriptive statistical analyses were conducted using STATA version 15.1 software (StataCorps LLC, College Station, TX, USA). Using Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC, USA), we conducted intention-to-treat analyses. Initially, we employed piece-wise linear mixed models to test on whether GV's changing trend was different between two time periods (0-3 months vs. 3-6 months based on the study design) in each arm (29). Specifically, we divided the study period into two segments according to study design: baseline to 3 months and 3 months to 6 months, then fitted the data using linear spline mixed models assuming different slopes within each segment but joined at 3 months. Fixed effects were included for the study arm, two time periods (0-3 and 3-6 months), and interactions of study arm

and time period. A random effect was included for the participants. Covariates of age and sex were included for adjustment. The differences of the temporal treatment effects between the two time periods (0-3 months vs. 3-6 months) in both arms were not significant. Therefore, we employed linear mixed models to analyze GV, in which time period (0-6 months), study arm, and the arm×time-period interactions were modeled as fixed effects and the participants were included as a random effect, while adjusting for covariates age and sex. With these models, we estimated the GV group means at 3 and 6 months and GV's changing trend in each treatment group, as well as performed the hypothesis tests to compare the group difference in terms of GV means at 3 and 6 months and GV's changing trend from baseline to 6 months. In all analyses, results were considered statistically significant if p-values were ≤ 0.05 using a two-sided test. We conducted post-hoc subgroup analyses separately by sex. There was an insufficient number of Hispanic participants to conduct subgroup analyses by self-reported ethnicity.

Sample size/ Power calculations

This manuscript examined tertiary outcomes of the parent study, the Personal Diet Study. Therefore, the sample size was not calculated for the purpose of the current manuscript. The Personal Diet Study was designed to detect a between group difference as small as 2% in weight loss (%) at the 6-month assessment, with the type I error set at 0.05, and a power of 80%. A sample of at least 164 participants (82 per group) was needed. Because we expected a 20% attrition, the parent study aimed to complete 200 baseline assessments.

Results

Study participants

Of the 269 participants who completed the study screening, 239 met eligibility criteria, 20 declined to participate, 15 were lost to follow-up, and 204 were randomized and completed the baseline assessment. Of those participants, 200 had HbA1c data (*Standardized* = 97, *Personalized* = 103) and 156 had least one day of CGM data (*Standardized* = 75, *Personalized* = 81) at baseline and were included in analyses. At baseline, the mean number of usable CGM days was 5.8 (SD = 2.1) for the *Standardized* diet arm, and 5.4 days for the *Personalized* diet arm (SD = 2.0). At 3-months it was 5.4 days (SD = 1.5) vs 5.6 days (SD = 1.7), and at 6-months it was 5.9 days (SD = 1.7) vs 5.5 days (SD = 1.9) for the *Standardized* diet vs *Personalized* diet arms respectively. There was no statistically significant difference in CGM observation days between groups. See **Figure 1** the CONSORT Diagram for more details. Study enrollment ended due to meeting enrollment requirements for the assessment of weight change outcome (primary outcome of the Personal Diet Study).

See **Table 1** for participants' characteristics. The final analysis sample consisted of 156 adults, the majority were female (66.5%, n = 105), had a Bachelor's degree or higher (69.5%, n = 110), and had an annual household income of at least $75,000 (54.4%, n = 86). The mean age was 59.1 years (SD = 10.7). Over half of the participants identified as White (55.7%, n = 88), 24.1% (n = 38) were Black, and most were non-Hispanic or non-Latino/a (83.5 %, n = 132). The average HbA1c at baseline was 5.81% (SD = 0.60).

Engagement with the intervention for participants included in the analytic sample.

On average, participants in the *Standardized* diet arm attended 71.1% (SD = 28.3) of the 14 group counseling sessions, and participants in the *Personalized* diet arm attended 74.5% of the sessions (SD = 26.6), with no between group differences (p = 0.95) (**Supplementary Figure**

2). In contrast, on average the percentage of days participants logged at least 50% of their daily caloric goal in the PNP mobile application, was 33.1% (SD = 34.2) for the *Standardized* diet arm, and 43.3% (SD = 33.8) for the *Personalized* diet arm (**Supplementary Figure 3**). This difference was statistically significant (p = 0.045). For both study arms, dietary self-monitoring adherence decreased substantially over time, and dropped to just over 20% during the final week of self-monitoring.

Glycemic Outcomes

Given that the slopes for 0-3 months, 3-6 months, and 0-6 months were the same, we only report the slope for 0-6 months here. See **Table 2** and **Figure 2** for results of linear mixed regressions. Except for CV obtained from CGM glucose measures, other measures of GV and HbA1c values were reduced for both study arms. No statistically significant between group differences were detected for any of the outcomes examined for the full sample or for the analysis stratified by sex. For instance, both groups experienced small, but statistically significant decreases in MAGE during the 6-months follow-up. MAGE decreased by 0.83 mg/dL per month for the *Standardized* diet arm (95% CI: 0.21, 1.46 mg/dL; p = 0.009), and 0.79 mg/dL per month for the *Personalized* diet arm (95% CI: 0.19, 1.39 mg/dL; p = 0.010), with no statistically significant between group differences (p = 0.93).

HbA1c decreased by 0.02% per month for the *Standardized* diet arm (95% CI: 0, 0.03%, p = 0.039), and 0.01% month for the *Personalized* diet arm (95% CI: 0, 0.03%, p = 0.057), with no statistically significant between group differences (p = 0.83). See **Supplementary Table 2** for changes from 0-3 months and 3-6 months and **Supplementary Tables 3** for analyses stratified by sex.

Discussion

While other studies demonstrate the potential clinical utility of precision nutrition algorithms for glycemic control (1, 19, 30), *Personalized* did not have greater reductions in measures of GV or HbA1c than *Standardized*. Using the PNP algorithm, Ben-Yacov et al. found that individuals with prediabetes randomized to a personalized postprandial glycemia-targeting diet had greater reductions in time above 140 mg/dL and HbA1c at 6 months than those following a Mediterranean diet (31). Compared to the current study, Ben-Yacov et al. reported greater reductions in HbA1c and mean CGM glucose in the personalized arm than what we found in our *Personalized* arm.

Our null findings may be partially explained by low dietary self-monitoring adherence rates, which were reported to be high by Ben-Yacov et al. Low adherence rates limited opportunities to obtain useful feedback that could have reduced PPGRs. Ben-Yacov et al. also provided participants with weight maintenance calorie targets and focused on glycemic control whereas the current study provided participants in both groups with calorie-restricted diets. Calorie restriction may have contributed to reduced PPGRs in both groups, which, in turn, limited our ability to detect between group differences in GV. In addition, participants were not selected on the basis of high baseline GV, perhaps limiting our ability to detect an effect.

We did not exclude individuals prescribed metformin because the glucose-lowering effect of this drug is thought to be mediated mainly by suppression of hepatic glucose production (32). However, metformin does appear to increase glucose uptake in skeletal muscle (33, 34), reduce intestinal glucose absorption (35), and alter gut microbiota in a manner that reduces

309 inflammation and improves insulin sensitivity (36), all of which could have dampened PPGRs
310 and limited our ability to detect an intervention effect.

311 Although more research is needed to determine the clinical significance of changes in
312 measures of GV, existing literature suggests that the within-group reductions in MAGE, as well
313 as in HbA1c, were not clinically meaningful (37, 38). Nonetheless, both arms had small, but
314 statistically significant reductions in MAGE and SD of glucose values. Mounting evidence
315 suggests that GV is associated with oxidative stress, which may contribute to β-cell deterioration
316 and the development and progression of T2D and its complications (39, 40). While the
317 hypothesized relationship between randomization assignment and GV was not observed, these
318 findings, in agreement with other research (41), support the importance of behavioral weight loss
319 interventions, such as those informed by the DPP, for those with prediabetes and moderately-
320 controlled T2D to reduce glycemic measures.

321 **Strengths and Limitations.** Our study had several limitations. Compared to the general
322 NYC population (42) and, more specifically, the NYC population with overweight and obesity
323 (43), White individuals (55.7%) were over-represented and Hispanic individuals (16.5%) and
324 male (33.5%) participants were under-represented in our sample. Our racial/ethnic distributions
325 are somewhat more representative than rates reported in a systematic review of 71 behavioral
326 weight loss trials featuring technology, in which an average of 73.2% of participants were White
327 and 7.7% were Hispanic (44). Representation of males (33.5%) in our study was slightly better
328 than the average male participation rate of 27% observed in a systematic review of 244 weight
329 loss studies (45). Nonetheless, generalizability of our findings is limited to a primarily White
330 female sample. Initially, the PNP algorithm was developed for and validated in an Israeli sample,
331 with later validation in a primarily White US sample (1). The predictive validity of the PNP

algorithm may differ in individuals of other races and ethnicities. Additional research is needed on how biosocial factors (e.g., stress, health behaviors, early life exposures, built environment, and social interactions) (46-48), affect the gut microbiome and their role in PPGR.

Although counseling session attendance was high for both study arms, dietary self-monitoring adherence was low overall and differentially lower in *Standardized* than *Personalized*. This may have occurred because participants in *Personalized* were more likely to perceive the feedback they received as useful for making dietary choices, which reinforced self-monitoring behavior. This study did not assess participants' health or digital literacy. Some participants experienced challenges in navigating the PNP app, which was optimized for an Israeli population. Difficulties with the app likely contributed to low adherence rates which, in-turn, limited exposure to the key feature of the intervention for participants in *Personalized* (23).

While a large proportion of participants had missing GV data at 3- and 6-month assessments, the linear mixed model allowed for any participant with at least one data point to be included in the analysis. A recent narrative review of 11 studies (5542 participants) employing CGM to guide diabetes management found compliance to be exceptionally high in prescribed wear times ranging from 3 to 168 days (49); our study used blinded CGMs for measurement only, which could have reduced motivation to comply. The study was also interrupted by the COVID-19 pandemic, requiring alterations in the measurement protocol which could have impacted the quality of our measures. For example, following onset of the COVID-19 pandemic, in-person measurement visits were suspended and videoconference-guided CGM self-insertion was employed. Because CGM data were exploratory in nature, we did not aggressively pursue return of complete CGM data. The study was also limited by the need to perform baseline measurements prior to randomization. In addition, because high GV was not part of the

355 enrollment criteria for this study, many participants had baseline values that were relatively low,
356 which may have limited our ability to see between-group differences. Finally, the Personal Diet
357 Study (21) was powered to detect a difference in weight loss and may not have been adequately
358 powered to detect differences in GV and HbA1c.

359 **Implications for research and practice.** Although the current study did not observe
360 between group differences in GV or HbA1c, both arms had reductions in MAGE and SD of
361 glucose values. Weight loss may be an effective approach to limit PPGR in patients with
362 prediabetes and moderately-controlled T2D. Whether reductions in GV were a result of weight
363 loss or greater adherence to dietary self-monitoring will be explored in future analyses. Future
364 studies testing the clinical efficacy of algorithm-based behavioral interventions to reduce PPGR
365 should enroll those with high baseline GV and consider strategies to enhance self-monitoring
366 behavior. Testing such interventions in the absence of calorie restriction may be a better design
367 to demonstrate an intervention effect on glycemia, and we have begun this research. Future
368 studies may benefit from using a dietary self-monitoring application optimized for the US
369 population, such as the DayTwo program, which also uses the PNP algorithm (DayTwo; Walnut
370 Creek, CA). Additional research is needed to assess the predictive validity of the PNP algorithm
371 in a more representative U.S. sample, and to examine how biosocial factors such as stress, health
372 behaviors, early life exposures, built environment, and social interactions affect the gut
373 microbiome and its role in PPGR (46-48).

374 A recent CGM study (50) found distinct glycemic phenotypes in those with prediabetes,
375 based on glucose values during the day relative to overnight. Future analyses on subgroups
376 stratified by their relative daytime and overnight glucose patterns may provide additional
377 markers to identify participants most likely to benefit from precision nutrition therapy. Subgroup

analyses are also planned to examine the role of dietary self-monitoring adherence on intervention effects.

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Author contributions

Conceptualization and design: MAS, LH, CP, MB, HL, MLP, MC, ES, AS, DSJ, NW, AMS

Collection and assembly of data: MLP, MC

Data analysis and interpretation: CW, AK, HL, SB

Manuscript writing, critical revision of manuscript for important intellectual content: All authors

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References

1. Mendes-Soares H, Raveh-Sadka T, Azulay S, Edens K, Ben-Shlomo Y, Cohen Y, et al. Assessment of a personalized approach to predicting postprandial glycemic responses to food among individuals without diabetes. JAMA Netw Open 2019;2(2):e188102-e.
2. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol J-P, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295(14):1681-7.
3. Kumar AA, Satheesh G, Vijayakumar G, Chandran M, Prabhu PR, Simon L, et al. Postprandial metabolism is impaired in overweight normoglycemic young adults without family history of diabetes. Sci Rep 2020;10(1):353. doi: 10.1038/s41598-019-57257-2.
4. Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, et al. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology 2002;35(2):373-9. doi: 10.1053/jhep.2002.30692.
5. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003;37(4):917-23. doi: 10.1053/jhep.2003.50161.
6. Huang Y, Cai X, Qiu M, Chen P, Tang H, Hu Y, et al. Prediabetes and the risk of cancer: a meta-analysis. Diabetologia 2014;57(11):2261-9. doi: 10.1007/s00125-014-3361-2.
7. DECODE Study Group, on behalf of the European Diabetes Epidemiology Group. Glucose Tolerance and cardiovascular mortality: Comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161(3):397-405. doi: 10.1001/archinte.161.3.397.
8. Barzilay JI, Spiekerman CF, Wahl PW, Kuller LH, Cushman M, Furberg CD, et al. Cardiovascular disease in older adults with glucose disorders: comparison of American Diabetes Association criteria for diabetes mellitus with WHO criteria. Lancet 1999;354(9179):622-5. doi: 10.1016/s0140-6736(98)12030-5.
9. Barr EL, Boyko EJ, Zimmet PZ, Wolfe R, Tonkin AM, Shaw JE. Continuous relationships between non-diabetic hyperglycaemia and both cardiovascular disease and all-cause mortality: the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study. Diabetologia 2009;52(3):415-24. doi: 10.1007/s00125-008-1246-y.
10. Takao T, Suka M, Yanagisawa H, Kasuga M. Thresholds for postprandial hyperglycemia and hypertriglyceridemia associated with increased mortality risk in type 2 diabetes patients: A real-world longitudinal study. J Diabetes Investig 2021;12(5):886-93. doi: 10.1111/jdi.13403.
11. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Abnormal glucose tolerance and the risk of cancer death in the United States. Am J Epidemiol 2003;157(12):1092-100. doi: 10.1093/aje/kwg100.
12. Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, Ludwig DS. Effects of a low–glycemic load vs low-fat diet in obese young adults: a randomized trial. JAMA 2007;297(19):2092-102.
13. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, et al. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: The DIETFITS randomized clinical trial. JAMA 2018;319(7):667-79. doi: 10.1001/jama.2018.0245.

14. Yancy WS, Jr., Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med 2004;140(10):769-77. doi: 10.7326/0003-4819-140-10-200405180-00006.
15. Bazzano LA, Hu T, Reynolds K, Yao L, Bunol C, Liu Y, et al. Effects of low-carbohydrate and low-fat diets: a randomized trial. Ann Intern Med 2014;161(5):309-18. doi: 10.7326/m14-0180.
16. Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348(21):2074-81. doi: 10.1056/NEJMoa022637.
17. Iqbal N, Vetter ML, Moore RH, Chittams JL, Dalton-Bakes CV, Dowd M, et al. Effects of a low-intensity intervention that prescribed a low-carbohydrate vs. a low-fat diet in obese, diabetic participants. Obesity (Silver Spring) 2010;18(9):1733-8. doi: 10.1038/oby.2009.460.
18. Brinkworth GD, Noakes M, Buckley JD, Keogh JB, Clifton PM. Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. Am J Clin Nutr 2009;90(1):23-32. doi: 10.3945/ajcn.2008.27326.
19. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell 2015;163(5):1079-94. doi: 10.1016/j.cell.2015.11.001.
20. Mendes-Soares H, Raveh-Sadka T, Azulay S, Ben-Shlomo Y, Cohen Y, Ofek T, et al. Model of personalized postprandial glycemic response to food developed for an Israeli cohort predicts responses in Midwestern American individuals. Am J Clin Nutr 2019;110(1):63-75. doi: 10.1093/ajcn/nqz028.
21. Popp CJ, Hu L, Kharmats AY, Curran M, Berube L, Wang C, et al. Effect of a personalized diet to reduce postprandial glycemic response vs a low-fat diet on weight loss in adults with abnormal glucose metabolism and obesity: A randomized clinical trial. JAMA Netw Open 2022;5(9):e2233760. doi: 10.1001/jamanetworkopen.2022.33760.
22. Popp CJ, St-Jules DE, Hu L, Ganguzza L, Illiano P, Curran M, et al. The rationale and design of the personal diet study, a randomized clinical trial evaluating a personalized approach to weight loss in individuals with pre-diabetes and early-stage type 2 diabetes. Contemp Clin Trials 2019;79:80-8. doi: 10.1016/j.cct.2019.03.001.
23. Hu L, Illiano P, Pompeii ML, Popp CJ, Kharmats AY, Curran M, et al. Challenges of conducting a remote behavioral weight loss study: Lessons learned and a practical guide. Contemp Clin Trials 2021;108:106522. doi: 10.1016/j.cct.2021.106522.
24. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr 1990;51(2):241-7. doi: 10.1093/ajcn/51.2.241.
25. Bandura A. Self-efficacy : the exercise of control. New York: W.H. Freeman and Company, 1997.
26. Diabetes Prevention Program Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 2002;25(12):2165-71. doi: 10.2337/diacare.25.12.2165.
27. Abbott. FreeStyle Libre 14 Day Indications and Important Safety Information. Internet: https://provider.myfreestyle.com/safety-information.html (accessed February 22,2022).

28. Kingsnorth AP, Whelan ME, Orme MW, Routen AC, Sherar LB, Esliger DW. Resistance to data loss from the Freestyle Libre: impact on glucose variability indices and recommendations for data analysis. Appl Physiol Nutr Metab 2021;46(2):148-54. doi: 10.1139/apnm-2020-0386.
29. Fitzmaurice GM LN, Ware JH,. Applied longitudinal analysis: John Wiley & Sons, 2012.
30. Berry SE, Valdes AM, Drew DA, Asnicar F, Mazidi M, Wolf J, et al. Human postprandial responses to food and potential for precision nutrition. Nat Med 2020;26(6):964-73. doi: 10.1038/s41591-020-0934-0.
31. Ben-Yacov O, Godneva A, Rein M, Shilo S, Kolobkov D, Koren N, et al. Personalized postprandial glucose response-targeting diet versus Mediterranean diet for glycemic control in prediabetes. Diabetes Care 2021;44(9):1980-91. doi: 10.2337/dc21-0162.
32. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) 2012;122(6):253-70. doi: 10.1042/cs20110386.
33. Lehtovirta M, Forsén B, Gullström M, Häggblom M, Eriksson JG, Taskinen MR, et al. Metabolic effects of metformin in patients with impaired glucose tolerance. Diabetic Med 2001;18(7):578-83. doi: 10.1046/j.1464-5491.2001.00539.x.
34. Sharoff CG, Hagobian TA, Malin SK, Chipkin SR, Yu H, Hirshman MF, et al. Combining short-term metformin treatment and one bout of exercise does not increase insulin action in insulin-resistant individuals. Am J Physiol Endocrinol Metab 2010;298(4):E815-23. doi: 10.1152/ajpendo.00517.2009.
35. Wu T, Xie C, Wu H, Jones KL, Horowitz M, Rayner CK. Metformin reduces the rate of small intestinal glucose absorption in type 2 diabetes. Diabetes Obes Metab 2017;19(2):290-3. doi: 10.1111/dom.12812.
36. He L. Metformin and systemic metabolism. Trends Pharmacol Sci 2020;41(11):868-81. doi: 10.1016/j.tips.2020.09.001.
37. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 6. Glycemic targets: Standards of care in diabetes-2023. Diabetes Care 2023;46(Suppl 1):S97-s110. doi: 10.2337/dc23-S006.
38. Monnier L, Colette C. Glycemic variability: should we and can we prevent it? Diabetes Care 2008;31 Suppl 2:S150-4. doi: 10.2337/dc08-s241.
39. Alfieri V, Myasoedova VA, Vinci MC, Rondinelli M, Songia P, Massaiu I, et al. The role of glycemic variability in cardiovascular disorders. Int J Mol Sci 2021;22(16). doi: 10.3390/ijms22168393.
40. Valente T, Arbex AK. Glycemic variability, oxidative stress, and impact on complications related to type 2 diabetes mellitus. Curr Diabetes Rev 2021;17(7):e071620183816. doi: 10.2174/1573399816666200716201550.
41. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393-403. doi: 10.1056/NEJMoa012512.
42. United States Census Bureau. Quick Facts New York City, New York. Internet: https://www.census.gov/quickfacts/newyorkcitynewyork (accessed November 13, 2022).
43. New York State Department of Health. New York City Health Data/EpiQuery Home/Diseases and Conditions. Internet: https://a816-health.nyc.gov/hdi/epiquery/visualizations?PageType=ts&PopulationSource=CHS&Topic=1&Subtopic=24 (accessed October 27, 2022).

44. Rosenbaum DL, Piers AD, Schumacher LM, Kase CA, Butryn ML. Racial and ethnic minority enrollment in randomized clinical trials of behavioural weight loss utilizing technology: a systematic review. Obes Rev 2017;18(7):808-17. doi: 10.1111/obr.12545.
45. Pagoto SL, Schneider KL, Oleski JL, Luciani JM, Bodenlos JS, Whited MC. Male inclusion in randomized controlled trials of lifestyle weight loss interventions. Obesity (Silver Spring) 2012;20(6):1234-9. doi: 10.1038/oby.2011.140.
46. Benezra A. Race in the microbiome. Sci Technol Human Values 2020;45(5):877-902. doi: 10.1177/0162243920911998.
47. Dowd JB, Renson A. "Under the skin" and into the gut: Social epidemiology of the microbiome. Curr Epidemiol Rep 2018;5(4):432-41. doi: 10.1007/s40471-018-0167-7.
48. Kim YS, Unno T, Kim BY, Park MS. Sex Differences in Gut Microbiota. World J Mens Health 2020;38(1):48-60. doi: 10.5534/wjmh.190009.
49. Taylor PJ, Thompson CH, Brinkworth GD. Effectiveness and acceptability of continuous glucose monitoring for type 2 diabetes management: A narrative review. J Diabetes Investig 2018;9(4):713-25. doi: 10.1111/jdi.12807.
50. Barua S, Sabharwal A, Glantz N, Conneely C, Larez A, Bevier W, et al. Dysglycemia in adults at risk for or living with non-insulin treated type 2 diabetes: Insights from continuous glucose monitoring. EClinicalMedicine 2021;35:100853. doi: 10.1016/j.eclinm.2021.100853.

Table 1. Participants' Sociodemographic and Other Baseline Characteristics (participants who withdrew or became ineligible after baseline are included)

	All Participants (n = 156)		Standardized Diet Arm (n = 75)		Personalized Diet Arm (n = 81)	
Sex (%, n)						
Male	33.5%	53	40.8%	31	26.8%	22
Female	66.5%	105	59.2%	45	73.2%	60
Age (mean, SD)	59.1	(10.7)	59.9	(10.6)	58.4	(10.8)
Race (%, n)						
White / Caucasian	55.7%	88	57.9%	44	53.7%	44
Black / African American	24.1%	38	25.0%	19	23.2%	19
Other	19.6%	31	17.1%	13	22.0%	18
Missing	0.6%	1			1.2%	1
Ethnicity (%, n)						
Non-Hispanic	83.5%	132	84.2%	64	82.9%	68
Hispanic	16.5%	26	15.8%	12	17.1%	14
Education (%, n)						
High school	13.3%	21	13.2%	10	13.4%	11
Associate degree	5.7%	9	7.9%	6	3.7%	3
Technical degree / certificate	5.7%	9	5.3%	4	6.1%	5
Bachelor's degree	25.9%	41	27.6%	21	24.4%	20
Master's degree	31.6%	50	25.0%	19	37.8%	31
Doctoral or Professional	12.0%	19	17.1%	13	7.3%	6
Missing	5.7%	9	3.9%	3	7.3%	6
Employed (%, n)						
No	26.6%	42	31.6%	24	22.0%	18
Yes	73.4%	116	68.4%	52	78.0%	64
Income (%, n)						
$10,000 - $19,999	1.9%	3	2.6%	2	1.2%	1
$20,000 - $29,999	1.9%	3	2.6%	2	1.2%	1
$30,000 - $39,999	5.1%	8	3.9%	3	6.1%	5
$40,000 - $49,999	5.1%	8	3.9%	3	6.1%	5
$50,000 - $74,999	19.0%	30	19.7%	15	18.3%	15
$75,000 - $99,999	15.2%	24	14.5%	11	15.9%	13
> $100,000	39.2%	62	40.8%	31	37.8%	31
Missing	12.7%	20	11.8%	9	13.4%	11
Baseline BMI (mean, SD)	33.7	(4.8)	33.0	(4.6)	34.3	(5.0)
Baseline HbA1c in % (mean, SD)	5.8	0.6	5.8	0.6	5.8	0.5
Baseline HbA1c category (%, n)						
< 6.5%	88.0%	139	85.5%	65	90.2%	74
≥ 6.5%	12.0%	19	14.5%	11	9.8%	8
MAGE (mg/dL)[1] (mean, SD)	51.9	(19.3)	53.0	(20.0)	51.0	(18.8)
CONGA (mg/dL)[1] (mean, SD)	91.5	(19.5)	93.5	(21.7)	89.6	(17.1)
Glucose: CV (mg/dL)[1] (mean, SD)	18.1	(4.6)	18.0	(4.1)	18.2	(5.0)
Glucose: SD (mg/dL)[1] (mean, SD)	19.0	(7.5)	19.4	(8.1)	18.6	(6.9)
Glucose: mean (mg/dL)[1] (mean, SD)	103.4	(21.5)	105.6	(24.1)	101.4	(18.6)

Note. Race and ethnicity are self-reported. SD = standard deviation, CONGA = continuous overall net glycemic action, MAGE = mean amplitude of glycemic excursions, CV = coefficient of variation, [1] data obtained at the baseline assessment.

Table 2. Results of Linear Mixed Regressions Intention to Treat Analysis: Change per month from baseline to the 6-month assessment in HbA1c and Glycemic Variability Outcomes

	Standardized Diet Arm				Personalized Diet Arm				Difference: Personalized minus Standardized Diet Arm			
	B	LL	UL	*p*	*B*	LL	UL	*p*	*B*	LL	UL	*p*
HbA1c %	-0.02	-0.03	0.00	0.039	-0.01	-0.03	0.00	0.057	0.00	-0.02	0.02	0.832
Mean Glucose Values (mg/dL)	-1.34	-2.18	-0.50	0.002	-0.78	-1.58	0.02	0.056	0.56	-0.60	1.72	0.345
SD of Glucose Values (mg/dL)	-0.30	-0.53	-0.07	0.010	-0.29	-0.51	-0.07	0.010	0.01	-0.30	0.33	0.928
CV of Glucose Values	0.04	-0.15	0.22	0.702	-0.15	-0.33	0.03	0.091	-0.19	-0.45	0.07	0.149
MAGE (mg/dL)	-0.83	-1.46	-0.21	0.009	-0.79	-1.39	-0.19	0.010	0.04	-0.82	0.91	0.925
CONGA (mg/dL)	-1.22	-2.00	-0.43	0.003	-0.62	-1.36	0.13	0.103	0.60	-0.48	1.68	0.275

Note. LL = lower level of a 95% confidence interval, UL = upper level of a 95% confidence interval, p = p-value, SD = standard deviation, CV = coefficient of variation, MAGE = Mean Amplitude of Glycemic Excursions, CONGA = Continuous overall net glycemic action. This intention to treat analysis was performed using a linear mixed regression adjusted for age and sex. For HbA1c: n=97, 44, and 35 for the *Standardized* diet arm; n=103, 53, and 40 for the *Personalized* diet arm, at baseline, 3 months, and 6 months assessments, respectively. For measures of glycemic variability (mean glucose values; SD of glucose values; CV of glucose values; MAGE; CONGA): n=75, 48, and 43 for the *Standardized* diet arm n=81, 55, and 49 for the *Personalized* diet arm, at baseline, 3 months, and 6 months, respectively

Figure 1. CONSORT Diagram

Figure 2. Results of Mixed Linear Regressions Intention to Treat Analysis: Changes in HbA1c, MAGE, and Coefficient of Variation with 95% Confidence Intervals

Note. *MAGE: Mean Amplitude of Glycemic Excursions.*
We conducted intention-to-treat analysis using piecewise linear mixed regression models controlling for age and sex. The black and grey bars in Figure 2 represent the 95% confidence interval.
The numbers of participants contributing data at each time point (0, 3, and 6 months) and for each study arm, are different due to missing values. For HbA1c: n=97, 44, and 35 for the *Standardized* diet arm; n=103, 53, and 40 for the *Personalized* diet arm, at baseline, 3 months, and 6 months assessments, respectively. For MAGE: n=75, 48, and 43 for the *Standardized* diet arm n=81, 55, and 49 for the *Personalized* diet arm, at baseline, 3 months, and 6 months, respectively. Coefficient of variation: n=75, 48, and 43 for the *Standardized* diet arm; n=81, 55, and 49 for the *Personalized* diet arm, at baseline, 3 months, and 6 months, respectively.

Enrollment

269 Assessed for eligibility

65 Excluded
- *30 Did not meet inclusion criteria*
- *20 Declined to participate*
- *15 Lost to follow-up*

204 Randomized

Baseline Assessment

105 Completed assessments
81 Had GV data and analyzed

99 Completed assessments
75 Had GV data and analyzed

Allocation

105 Allocated to **personalized group**
100 Received allocation intervention
5 Did not receive allocation intervention
- 3 Withdrew
  - *2 Time commitment*
  - *1 Unwilling to complete profiling*
- 1 Ineligible
  - *1 Prescribed exclusionary medication*
- 1 Lost to follow up

99 Allocated to **standardized group**
96 Received allocation intervention
3 Did not receive allocation intervention
- 2 Withdrew
  - *1 Time commitment*
  - *1 Unknown*
- 1 Ineligible
  - *1 Significant weight loss prior to intervention*
- 0 Lost to follow up

Follow up - 3 months

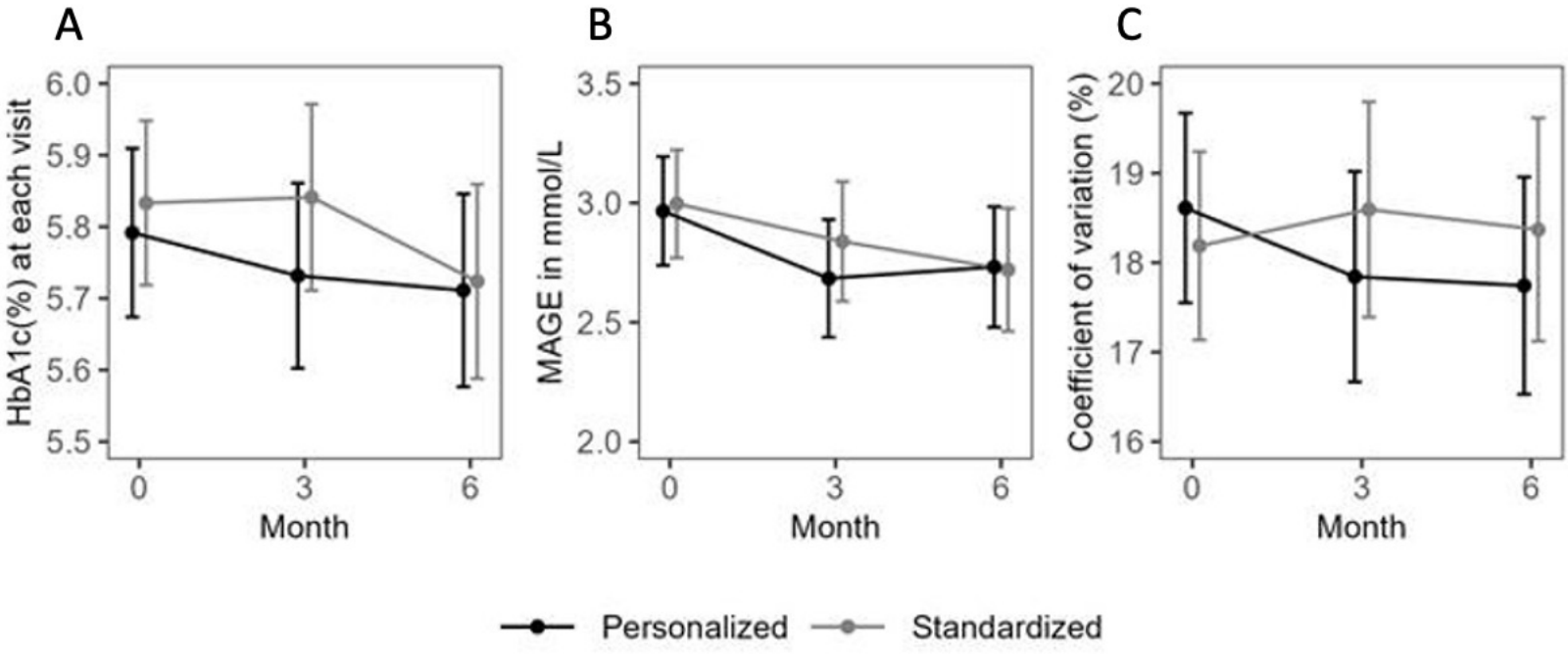
100 Expected to complete assessment
55 Had GV data and analyzed
45 Excluded from analysis
- 8 Participant withdrawal
  - *1 Cancer diagnosis*
  - *3 Time commitment*
  - *4 Unspecified*
- 2 Investigator withdrawal
  - *1 Became pregnant*
  - *2 Prescribed exclusionary medications*
- 3 Lost to follow up
- 32 No GV data

96 Expected to complete assessment
48 Had GV data and analyzed
48 Excluded from analysis
- 12 Participant withdrawal
  - *3 Developed medical condition*
  - *2 Time commitment*
  - *1 Relocation*
  - *6 Unspecified*
- 1 Investigator withdrawal
  - *1 Participation in another study*
- 5 Lost to follow up
- 30 No GV data

Follow up - 6 months

87 Expected to Complete Assessment
49 Had GV data and analyzed
38 Excluded from analysis
- 1 Participant withdrawal
  - *1 Medical condition (unspecified)*
- 0 Investigator withdrawal
- 0 Lost to follow up
- 37 No GV data

78 Expected to Complete Assessment
43 Had GV data and analyzed
35 Excluded from analysis
- 1 Participant withdrawal
  - *1 Unspecified*
- 0 Investigator withdrawal
- 0 Lost to follow up
- 34 No GV data


A
B
C
HbA1c(%) at each visit
6.0
5.9
5.8
5.7
5.6
5.5
MAGE in mmol/L
3.5
3.0
2.5
2.0
Coefficient of variation (%)
20
19
18
17
16
0
3
6
Month
Personalized
Standardized