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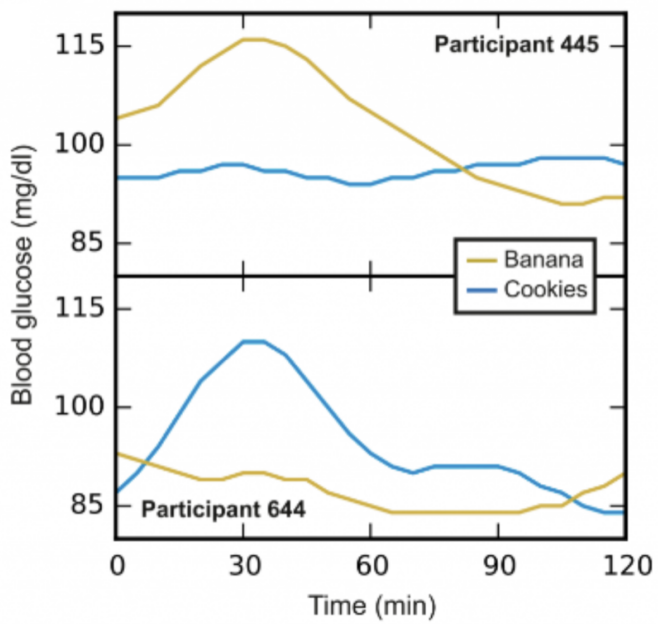
Kharmats AY, Popp C, Hu L, Berube L, Curran M, Wang C, Pompeii ML, Li H, Bergman M, St-Jules DE, Segal E, Schoenthaler A, Williams N, Schmidt AM, Barua S, Sevick MA. A randomized clinical trial comparing low-fat with precision nutrition-based diets for weight loss: impact on glycemic variability and HbA1c. Am J Clin Nutr. 2023 Aug;118(2):443-451.

What We Know, Think We Know, or Are Starting to Know

The concept of "personalised nutrition" [PN] has leapt to the fore of nutrition science, with the promise that we can use patient data to design predictive interventions that are more individualised, and therefore more effective [1,2]. Proponents of PN argue that such targeted, individualised nutrition advice offers advantages over broader, population-level dietary recommendations [2].

Within the overall research area of PN, glyceamic control has been the predominant focus and primary outcome measure of all the landmark studies to date [3-5]. A major emphasis of the findings from these trials is the inter-individual variation in post-prandial glucose responses to the same foods, and often some counterintuitive findings.

For example, the **figure** below is taken from one of the landmark PN trials by Zeevi et al. [4] in 2015; the figure compares two individual participants to either cookies [blue line] or a banana [yellow line]. As you can see, "Participant 445" on the top graph had a much worse post-prandial response to the banana over a 2 h period.



In the UK PREDICT study, similar inter-individual variation was observed, however, post-prandial glucose responses were also strongly influenced by well-established variables influencing glycaemic control, including meal composition, meal timing, exercise, and sleep [3].

Overall, while there is no doubt some fascinating findings exist in the PN research, whether using algorithms to predict effectiveness of dietary interventions, and whether the predictiveness is more advantageous than standard dietary advice, is far from a proven case.

The fact that PN is already being hastily commercialised means that it is important that we have a sharp eye for the true strength of the evidence in this area. The present study is the most recent trial comparing PN to standard dietary advice in a "head-to-head" intervention.

The Study

The Personal Diet Study was a randomised, parallel-group [i.e., both groups ran at the same time] controlled trial comparing two dietary interventions in participants with prediabetes or type-2 diabetes [T2D]. Participants were randomised to one of the two interventions:

- **Pesonalised Diet [PD]**: Participants in this group were provided with an app which contained colour-coded meal scores, based on their predicted pos-prandial glucose response from an algorithm. The meal scores were coded as "excellent", "very good", "good", "bad" and "very bad". Participants were advised to make food choices according to the meal scores. A ~500kcal/d energy deficit was targeted, aiming to achieve ~7% bodyweight loss.
- **Standardised Diet [SD]**: Participants in this group were also provided with an app for tracking daily energy and macronutrient intakes, with the aim of <25% energy from total fat. A ~500kcal/d energy deficit was also targeted, aiming to achieve ~7% bodyweight loss.

As part of the intervention, all participants were provided with a group-based, dietitian-led behavioural counselling programme for 1 h that occurred weekly for the first month of the study, followed by every other week for 20-weeks.

All participants wore continuous glucose monitors [CGMs] and had blood samples taken to measure HbA1c at baseline, 3-months, and 6-months timepoints. The primary outcome of the study was the Mean Amplitude of Glycaemic Excursions [MAGE; see ***Geek Box** below for further details]. Secondary outcomes included other measures of glycaemic variability and HbA1c.

*Geek Box: Measuring Glycaemic Variability

Typically, there are several standardised measures that are used to investigate glycaemic control, e.g., fasting plasma glucose, or 2 h post-prandial glucose response to an oral glucose tolerance test [OGTT]. However, while these measures may capture glycaemic control, they may not necessarily capture glycaemic variability. The term "glycaemic variability [GV]" broadly refers to swings in blood glucose levels, which may include blood glucose oscillations that occur throughout the day [i.e., post-prandial excursions], or blood glucose fluctuations that occur at the same time on different days.

The broad definition of GV considers between-day and withing-day glycaemic excursions, including episodes of hyperglycaemia and hypoglycaemia. Glycaemic variability may be influenced by several factors, including circadian timing of glucose rhythms and glucose tolerance, meal timing and meal composition, and other environmental factors, e.g., sleep. Some have argued that GV may not be adequately captured by measures like HbA1c, particularly in individuals who have good glycaemic control. Using CGM data has allowed for other measures of GV to be developed, including:

- ***MAGE** [Mean Amplitude of Glycaemic Excursions]: designed to capture mealtime-related glucose excursions, assessed as glucose levels 1-SD above or below the 24 h average minimum or maximum, respectively.*
- ***CONGA** [Continuous Overlapping Net Glycaemic Action]: describes **intra-day** glycaemic variation as difference between current time-period of observation [e.g., 60min or 120min] and previous same time-period.*
- ***MODD** [Mean of Daily Differences]: Compares glucose at same time point to determine similarity in patterns of glucose fluctuations **inter-day**.*

However, it is important to note that these measures have not been fully validated for their ability to predict outcomes more accurately over standardised glycaemic measures such as fasting plasma glucose or HbA1c. These measures are primarily used in clinical dietetic management of diabetes, which is where the utility of CGMs is confined beyond research, for now.

Results: 204 participants were randomised, of which there was CGM data available for 156 participants [*n* = 81 in the PD and *n* = 75 in the SD], which formed the final sample size for the present study. ~66% of participants were female, average baseline age was ~59yrs, and the ethnicity distribution in the study sample was 55% White and 24% Black [and 19% "Other"]. Average baseline HbA1c was 5.81% in the "high risk" but normal range.

***Primary Outcome – MAGE*:** Over 6-months there were no significant differences in the MAGE between groups; the PD group showed an average monthly decrease of 0.79mg/dL [95% CI, 0.19 to 1.39mg/dL], while the SD group showed an average monthly decrease of 0.83mg/dL [95% CI, 0.21 to 1.46mg/dL]. There were no significant differences in any other measures of glycaemic variability.

***Secondary Outcome – HbA1c*:** Over 6-months there were no significant differences in HbA1c between groups; the PD group showed an average monthly decrease of 0.01% [95% CI, 0 to 0.03%], while the SD group showed an average monthly decrease of 0.02%[95% CI, 0 to 0.03%].

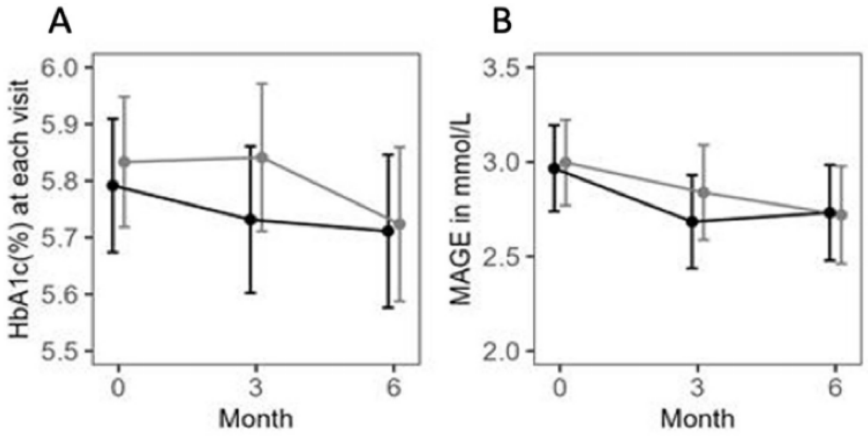


*Figure from the paper [Personalised Diet = **black bars**; Standardised Diet = **grey bars**] showing [**left**] changes in HbA1c between groups, and [right] changes in the MAGE between groups, at each respective timepoint of the study. While the graph gives an appearance of some differences, this is illusory; for example, the left Y-axis for HbA1c is showing differences within a 0.1% range. Even if the actual lines appear to diverge, the upper and lower arms of the confidence intervals all overlap, and the mean [**circle**] of each group at each time point is within the confidence intervals of the other group.*

Engagement of Participants in Behavioural Counselling Programme*:** For the group counselling sessions, average attendance rate was 74.5% and 71.1% in the PD and SD groups, respectively, with no significant differences between groups. The average number of days during the study where ≥50% of a participant's calorie goal was logged was 43.3% and 33.1% in the PD and SD groups, respectively [discussed further under ***Interesting Finding, below].

The Critical Breakdown

Pros: The study was preregistered, and there are no apparent deviations from protocol. Participants were randomly allocated to either diet in equal block sizes, and remained blinded to their allocated diet group until week 5 of the intervention. The sample size was good relative to previous research and is one of the larger studies comparing PN to standard advice in a direct intervention. Both groups were given equal treatment for the behavioural counselling aspect of the intervention. The primary and secondary outcomes were clearly stated. An average of 5-days of CGM data per participant was available for both diet groups for analysis at each timepoint of the study.

Cons: While participants were randomised, their allocation was preassigned due to additional requirements of assessment for the PD group; this may have resulted in some imbalances evident between groups, e.g., the groups were very poorly balanced for proportions of male and female participants. Although 204 participants were randomised, CGM data was only available for 156 participants, and while the statistical approach accounted for missing data it would not entirely eliminate the lower power for the CGM outcomes. Participants were advised to engage in 150min/week of moderate-to-vigorous physical activity, but this was not measured during the study, and it is possible that any differences in physical activity may have influenced glycaemic outcomes. Finally, the highly educated, wealthy study sample may not generalise to the wider U.S. population.

Key Characteristic

The present study used the algorithm that was derived from an Israeli population cohort of 800 participants [(4)]. Using the same methods employed in the Israeli study, the algorithm data generation was applied in a U.S. population to determine whether the algorithm could be validated for use in the U.S. [(6)].

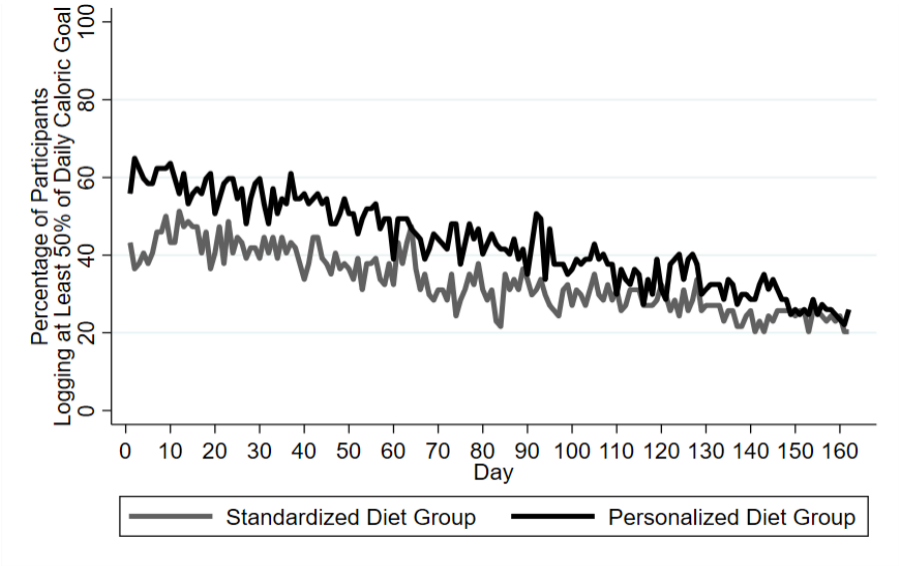
However, the predictive value of the algorithm showed a weaker correlation with actual measured glycaemic responses in the U.S. cohort compared to the Israeli cohort. And a major limitation of the U.S. validation study is that no data on the ethnicity characteristics of the participants was presented [(6)].

This highlights one of the major limitations of the current PN research, which is the lack of replication in some key outcomes of interest. For example, while the composition of the gut microbiota was found to mediate post-prandial glucose responses in the Israeli study, it did not mediate glucose responsiveness in the UK-based PREDICT study [(3,4)].

The present study further indicates that insofar as PN is predicated upon the supposed advantage of accuracy, that accuracy may be less than the hype suggests, and there may be little added advantage over more general dietary interventions.

Interesting Finding

To be fair to the PN paradigm, there is one outcome from the present study that may, at least in part, explain the underwhelming results.



The adherence in both diet groups was very poor, evident in the figure above which shows the percentage of participants logging ≥50% of their daily calorie goal. As we can clearly see, self-monitoring of their dietary adherence eroded steadily over time, bottoming out at ~20% by the end of the study in both groups.

This is reflective of a well-established characteristic of dietary interventions, which is low adherence, and adherence is strongly associated with effectiveness of dietary interventions [(7)]. And in clinical trials of pharmacological treatments, high non-adherence rates result in weakened ability to detect true differences between treatments [(8)]. The present study indicates that PN is no different and appears to offer little additional advantage to the challenge of low adherence to dietary interventions.

Relevance

The present study was the first intervention in a U.S. population following the validation of the Israeli cohort algorithm, and overall has produced underwhelming results. The primary outcome of the overall study was weight loss, which was reported in another publication; the SD group lost 4.3% of bodyweight over 6-months compared to 3.2% in the PD group [(9)].

The strength of the correlation between predicted and measured post-prandial glucose responses in the U.S. validation cohort [an R = 0.59 where 1.0 is a perfect positive correlation] is similar to the strength of correlations for many nutrients in nutritional epidemiology [(10)]. Bear in mind, however, that nutritional epidemiology is routinely criticised for such correlations, while PN continues to be venerated as a new dawn of accuracy for nutrition research and practice.

Interestingly, the Israeli intervention study by Zeevi et al. [(4)] study that followed from the algorithm validation also showed no difference between the algorithm-derived PN diet or a dietitian-led consultation in predicting post-prandial glucose responses in

participants. Based on the same algorithm, the present study has at least replicated that finding in showing no superiority for PN compared to standard dietary advice.

To date, the only study to emphatically demonstrate an advantage to PN was another study from the Israeli group, which compared a PN diet based on the same algorithm to a Mediterranean diet in participants with prediabetes [(5)]. The PN diet lowered HbA1c by 0.16% over 6-months compared to a 0.08% decrease on the Mediterranean diet. While this constituted a significant between-group difference, the actual magnitude of the decrease from a clinical significance standpoint is paltry.

Overall, there is little evidential support for any inherent advantage of algorithm-based PN interventions for improving glycaemic control, particularly when stacked up against current knowledge of factors that influence post-prandial glucose responses, e.g., meal composition, meal timing, exercise, sleep, etc. [(3)].

Application to Practice

Ultimately, once we strip the sheen of tech and the "sexiness" of machine-learning away, we are left with recommendations for overall glycaemic control, for example good sleep, exercise, having a breakfast meal, and daily energy load, that would already be in any nutrition professional's toolbox. And we can confidently state that the rush to commercialise PN is putting the money-spinning cart before the evidential horse. Stay frosty to the lofty claims.

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