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Differential effects of lifestyle interventions on continuous glucose monitoring metrics in persons with type 2 diabetes: Potential for personalised treatment

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Abstract

Aims: The effects of lifestyle on glucose metabolism significantly differ between individuals. Hyperglycaemia in type 2 diabetes is driven by tissue-specific insulin resistance and reduced beta-cell capacity, whose relative contribution varies between persons, potentially affecting the impact of lifestyle interventions. We quantified effects of lifestyle on continuously measured glucose (CGM) metrics and evaluated how these differ between type 2 diabetes subtypes.

Materials and Methods: This is a repeated-measures study with 40 persons with type 2 diabetes. Participants wore a CGM for 11 self-monitoring periods of 4 days, of which 3 were control and 4 were duplicated intervention periods (2× low carbohydrate diet, 2× Mediterranean diet, 2× walking after each meal and 2× ‘active day’ (hourly 5-min exercise bouts)). The order of the intervention periods was randomised. Tissue-specific insulin resistance and beta-cell function were quantified using an OGTT and were used to assign participants to diabetes subtypes or ‘diabetypes’. A linear mixed effects model quantified lifestyle impact on CGM metrics.

Results: On average, a low carbohydrate diet, walking after meals, and an active day, but not the Mediterranean diet, resulted in lower mean glucose (−0.95 (CI: −1.13, −0.77), −0.28 (CI: −0.46, −0.1), −0.2 (CI: −0.38, −0.02) and −0.13 (CI: −0.13, 0.05) mmol/L, respectively) as compared with control (8.73 mmol/L, CI: 8.02–9.44) in participants who did not restrict carbohydrate intake at baseline. Preliminary analysis suggests the magnitude and direction of effects may vary between diabetypes.

Conclusions: Traditional lifestyle interventions improved CGM metrics within 4 days. Preliminary analysis suggests the effects may vary depending on the diabetes phenotype.

KEYWORDS

continuous glucose monitoring, diabetes mellitus type 2, lifestyle intervention, multilevel modelling, personalised health, real-life setting

1 | INTRODUCTION

Type 2 diabetes is a chronic metabolic disorder characterised by insulin resistance and dysglycaemia. Lifestyle modifications, including adopting a healthy diet, increasing physical activity, and losing weight, can improve glycaemic control and insulin sensitivity, thereby mitigating diabetes-related complications.^{1–3} The Look AHEAD trial has demonstrated that adopting a healthier lifestyle can delay progression of type 2 diabetes.⁴ However, the impact of lifestyle interventions varies greatly between individuals, with high interindividual variability in the postprandial glucose response to identical foods,^{5,6} and differential responses to dietary interventions between normoglycaemic and (pre-)diabetic people.⁷ In view of the inherent heterogeneity of the disease,⁸ it seems quite conceivable that the efficacy of lifestyle interventions is not uniform across individuals with type 2 diabetes, and that personalisation of dietary advice or physical activity regime may be required for optimal glycaemic control.⁹

Most lifestyle intervention studies so far were medium to long-term, group-based, and focus predominantly on HbA1c as a measure of glycaemic control. Even though HbA1c offers valuable insight in long-term glucose control, it does not reflect acute glycaemic excursions and events such as hypoglycaemia or postprandial hyperglycaemia.¹⁰ Since the introduction of continuous glucose monitoring (CGM), it has been established that CGM-derived measures of glycaemic control are clinically relevant^{10,11} and linked to all-cause mortality and risk of macro- and microvascular complications.^{12,13} A CGM system provides real-time (interstitial) glucose concentrations and can be used to calculate widely accepted metrics that reflect not only mean glucose but also measures of glycaemic variability as well as time in, below, and above target ranges.^{10,11} CGM can thus provide insight into short-term effects of lifestyle on glycaemic control and may serve as an early intervention tool to determine appropriate lifestyle modifications.

The main aim of this study was to explore the (sub)acute effects of distinct lifestyle interventions on CGM metrics in people with T2D.

From earlier work, we know short-term glycaemic variations may differ between diabetic phenotypes, as the severity of insulin resistance may differ between various insulin-sensitive tissues.¹⁴ It has been suggested that the diabetic phenotype or 'diabetype', based on the predominant location of insulin resistance (i.e., muscle, liver, or both) and the remaining capacity of beta-cells to produce insulin, may affect the response to different dietary interventions.^{15–17} Also, physical exercise may be especially effective in improving glycaemic control in people who are predominantly affected by muscle insulin resistance.¹⁸ Insight into the differential effects of lifestyle interventions on glucose management among individuals with distinct diabetypes may contribute to more personalised lifestyle recommendations. Therefore, as an exploratory post hoc analysis, we also assessed the impact of the 'diabetype' in this context.

2 | MATERIALS AND METHODS

2.1 | Study population

Men and women with type 2 diabetes, as diagnosed by a physician, using either lifestyle and/or metformin for managing glycaemic control were recruited via general practitioners (GPs), social media and newspaper advertisements. Exactly 63 candidates were screened for eligibility by a study physician and deemed eligible if they met the following inclusion criteria: aged 18–80 years, Body Mass Index (BMI) 25–40 kg/m², preferably <35 kg/m², insulin-naïve, able and willing to provide informed consent, and willing to comply with all study procedures. The exclusion criteria were unavailability for longer periods during the study, history of or planned (bariatric) surgery or MRI in the next 6 months, chronic medical conditions or medication use interfering with glucose metabolism, chronic anaemia, use of antibiotics or fertility treatments within 3 months before participation, pregnancy or pregnancy wish, regular alcohol (>4 glasses) or recreational drug use, skin allergy or eczema, and Coeliac or Crohn's disease. Out of 63, 21 were excluded (medication use $n = 10$; BMI $n = 4$; age $n = 3$; no time $n = 1$; recent weight loss >5 kg $n = 1$; too much alcohol consumption $n = 1$; not able to follow interventions $n = 1$) and 42 started the study. During the study there was one drop-out due to starting on gliclazide. Baseline characteristics are shown in Table 1. A simulation study using a random effects approach was performed to determine the required sample size, which showed that it is important to repeat the conditions (as described in the design), and that with 40 participants there is over a 90% probability of detecting a true (average) difference of 1 mmol/L between interventions.

2.2 | Study procedures

During the start visit, anthropometry (height (first visit only), body-weight, waist- and hip circumference) and blood pressure were measured according to standard operating procedures, and online questionnaires were completed.

Hereafter, each participant followed 11 four-day monitoring periods spread out over 27 weeks in a randomised repeated measures design to balance out order effects of the different interventions. These included three 4-day control periods, during which glucose was monitored in daily life, while the impact of two dietary (low carbohydrate diet and Mediterranean diet) and two exercise-based interventions (walk after meal and active day) on CGM metrics was measured during eight 4-day intervention periods (Figure 1). During all periods, participants used an (unblinded) continuous glucose monitor (CGM), monitored physical activity and sleep, and registered food intake, medication use and wellbeing via a custom smartphone application. Participants calibrated their CGM system every morning using a finger prick and manual blood glucose measurement device (Accu-Chek Instant, Roche, Basel, Switzerland).

At the end of or just before each control period (week 2, 13 and 24), participants came to the clinic for an Oral Glucose Tolerance Test

	<i>n</i>	Mean	SD
Sex (male/female)	22/19		
Education (lower/higher)	15/26		
Treatment (yes/no metformin)	25/16		
Age (year)		62.3	7.2
Diabetes duration (year)		9.7	6.5
BMI (kg/m ²)		29.2	3.8
HbA1c (% (mmol/mol))		7.1 (54.5)	3.5 (14.8)
Insulin fasting (mU/L)		12.05	8.90
C-peptide fasting (nmol/L)		0.87	0.42
Hepatic Insulin Resistance Index (HIRI)		1812	1362
Muscle Insulin Sensitivity Index (MISI)		−3.60	4.23
Disposition Index (DI)		0.72	0.53
Total cholesterol (mmol/L)		4.67	1.13
LDL cholesterol (mmol/L)		2.91	1.00
Triglycerides (mmol/L)		1.46	0.72
C-Reactive Protein (CRP) (mg/L)		2.27	2.49
Systolic blood pressure (mmHg)		160.4	17.9
Diastolic blood pressure (mmHg)		91.2	14.4

TABLE 1 Baseline characteristics of 41 participants with type 2 diabetes mellitus.

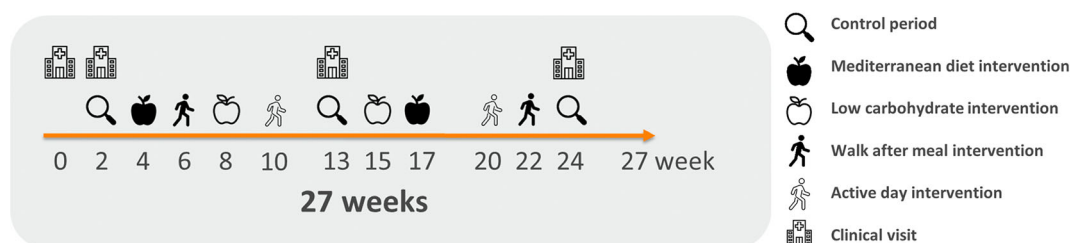


FIGURE 1 Schematic overview of the study design. All self-monitoring periods (control period, Mediterranean diet intervention, low carbohydrate intervention, walk after meal intervention, active day intervention) lasted 4 days and were followed by at least 1 week of wash-out. The order of the interventions was randomised per participant. Clinical visits for oral glucose tolerance testing took place right after the control periods.

(OGTT). After the first control period (week 2), each participant underwent four lifestyle interventions in a randomised order. The second control period was planned after the first series of intervention periods (week 13), after which all four interventions were repeated in a randomised order. Subsequently, the last control period and OGTT were performed (week 24). All control and intervention periods were separated by at least 1 week wash-out period. The study ended with a clinical visit during which anthropometric and blood pressure measurements were repeated (week 27). Helpdesk support was available throughout the study, and follow-up phone calls were scheduled before and after each monitoring period to enhance compliance with self-monitoring and the interventions. The study protocol was approved by the Medical Ethics Committee Brabant (NL70771.028.19), performed in accordance with the Declaration of Helsinki and good clinical practice and registered at the Dutch Trial Register: NL7848. All participants provided written informed consent.

2.3 | Interventions

During the 'Active day' (AD) intervention, participants were asked to perform moderate to intense physical exercise (e.g., brisk walking, climbing the stairs or knee bends) for 5 min every hour between 09:00 and 17:00 h to reduce sedentary time. During the 'Walk after meal' (WaM) intervention, participants were asked to walk for 15 min after each breakfast, lunch and dinner to reduce postprandial glucose levels. During the 'Low carbohydrate diet' (LC) intervention, participants were instructed not to exceed a maximum intake of 100 g of carbohydrates a day. During the 'Mediterranean diet' (Med) intervention, participants were instructed to eat a diet high in fruits, vegetables, nuts, fish, whole grains and olive oil. During both dietary interventions, for breakfast, lunch and snacks participants received fitting recipes, and for dinner participants received meal boxes with unprocessed food and recipes for cooking at home from Ekomenu (Amsterdam, The Netherlands).

2.4 | Measurements

2.4.1 | Self-monitoring devices

The Dexcom G6 Continuous Glucose Monitoring (CGM) System (Dexcom Inc., San Diego) measured interstitial glucose concentration every 5 min. Participants applied the Dexcom G6 sensor on the upper arm 1 day before the start of each monitoring period to allow for stabilisation of the sensor.

Participants used the HowAml app (TNO, Leiden, The Netherlands)¹⁹ for collecting food intake data. The HowAml app used the FatSecret food database (Secret Industries Pty Ltd., Victoria, Australia) to access detailed food and nutrition data and connected to a custom, parallel back-end database to record food intake and time stamp for each meal.

The Fitbit Charge 3 activity tracker (Fitbit, San Francisco, CA) was used to measure daily physical activity in Metabolic Equivalent of Tasks (METs) and sleep in hours.

2.4.2 | Oral glucose tolerance test and diabetyping

An OGTT was performed to assess plasma glucose and insulin response to a standardised glucose solution (75 g of glucose dissolved in water). Venous blood samples were taken before as well as 30, 60, 90, and 120 min after consumption of the sugar water. Blood glucose and insulin concentrations were used to calculate the following three indices used for retrospective 'diabetyping' of participants: (1) the hepatic insulin resistance index (HIRI); (2) the muscle insulin sensitivity index (MISI) and (3) the disposition index (DI) as a measure of pancreatic beta-cell function.^{14,20–22} A combination of liver and/or muscle IR with or without impaired beta-cell function (BCF) resulted in a total of eight possible subgroups ('diabetypes').²³

2.4.3 | Questionnaires

Questionnaires on demographics, lifestyle, diabetes duration, and treatment were completed via an online portal. Regular dietary intake before study participation was assessed using the online 183-item Food Frequency Questionnaire (FFQ) developed by Wageningen University and Research.^{24,25}

2.5 | Statistical analysis

Statistical analyses were performed using R software.²⁶ To check compliance with the lifestyle interventions, compliance scores for the LC, AD, and WaM interventions were calculated. For the Med intervention, no compliance score was calculated as adherence to the Mediterranean diet is not easily quantifiable. For the LC intervention, compliance was defined as days during which carbohydrates (CHO) contributed <26% to total caloric intake.^{27,28} For the WaM

intervention, compliance was defined as days with ≥ 4 periods of physical activity for ≥ 10 min. For the AD intervention, compliance was defined as days with ≤ 4 sedentary periods of ≥ 2 h of inactivity; four consecutive sedentary periods of 2 h or more were interpreted as sleep.

CGM metrics were calculated per person, per 4-day measurement period. Mean glucose, coefficient of variation (CV), time in range (TIR; >3.9 and <10.0 mmol/L), time above range level 1 (TAR-L1; ≥ 10.0 and <13.9 mmol/L), time above range level 2 (TAR-L2; ≥ 13.9 mmol/L), time below range level 1 (TBR-L1; >3.0 and ≤ 3.9 mmol/L), time below range level 2 (TBR-L2; ≤ 3.0 mmol/L), and mean amplitude of glucose excursions (MAGE) were calculated according to an international consensus statement.¹⁰

A random effects multilevel model was used to quantify the effects of the four lifestyle interventions on CGM metrics with participant as a random effect (null models). Time was tested as a covariate, but this showed no effect on CGM metrics or model improvement. This indicates that our assumption that 4-day interventions followed by at least a week of wash-out indeed avoided longer-term effects and carry-over effects between interventions. Subsequently, a binary variable reflecting CHO consumption before the study, as assessed by FFQ, was added to the null model. Specifically, the study population was split into two groups, a 'normal carb' group consuming more than 26% of calories as CHO at baseline, and a 'low carb' group eating <26% of calories as CHO.^{27,28} Adding this variable improved the performance of all models for CGM metrics (final models).

2.6 | Post hoc analysis

As a post hoc analysis, the impact of further adding diabetype and interaction effects on model performance was assessed (post hoc models) using random effects models as well. Only diabetypes assigned to at least 10 participants at any point in time during the study were included in the models to allow for sufficient power in the models. As for some individuals the diabetype changed during the study (supposedly affected by lifestyle interventions), the diabetype defined by the most recent OGTT was used for the next monitoring period in the model. Diabetypes assigned to at least 10 participants were (1) isolated impaired BCF (PB; $n = 16$); (2) hepatic IR and impaired BCF (PB-HIR; $n = 30$); and (3) both hepatic and muscle IR and impaired BCF (PB-HMIR; $n = 11$), where 17 persons had two distinct phenotypes over time. Model performance for all CGM metrics but TAR-L2 improved significantly when the three most common diabetypes, PB, PB-HIR and PB-HMIR were added (Table S1). Therefore, separate models were made for each diabetype assigned to at least 10 participants during the entire study to assess which lifestyle interventions sorted the most beneficial effects for each of the three diabetypes. The amount of CHO consumed at baseline (as measured using the FFQ) interacted with intervention effects on CGM metrics and was therefore also included in the models for the PB group and PB-HIR group. In the PB-HMIR group there was only one participant with a low CHO intake at baseline, who was therefore excluded from

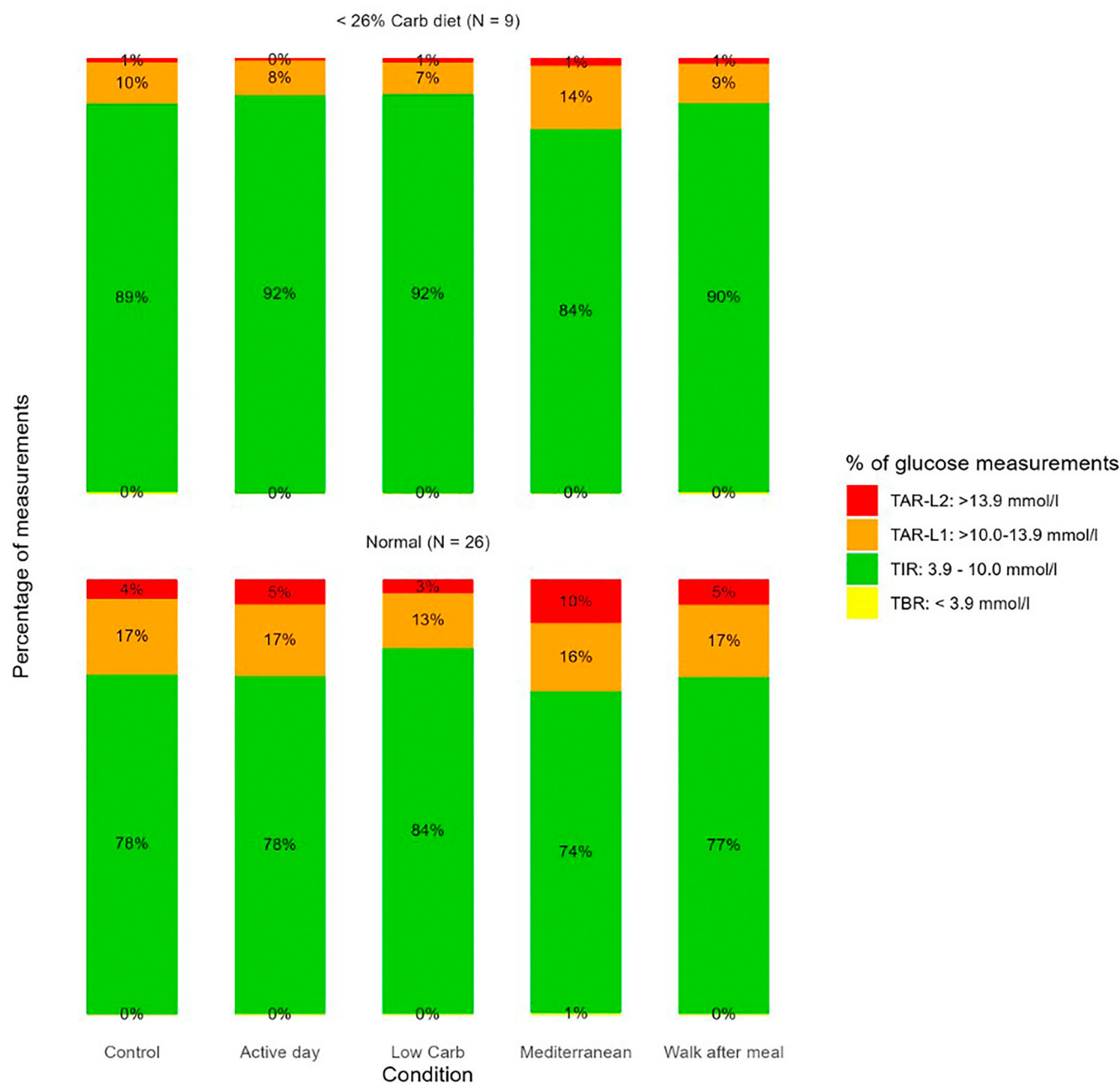


FIGURE 2 Average time spent in range for control and intervention periods. Time in Range (TIR), Time below range (TBR) and Time above range (TAR) are expressed as an average percentage of total time spent in this range for participants consuming >26% of calories from carbohydrates at baseline (lower bars; N = 26) and for participants consuming <26% of calories from carbohydrates at baseline (upper bars; N = 9).

the analysis. The final models included intercept, intervention, and for two subgroups (PB and PB-HIR) also CHO consumption at baseline as well as its interaction with intervention as fixed factors, and participant as a random effect.

3 | RESULTS

Significance is assessed for a two-sided alpha of 0.05, or a 95% confidence level (CI). This means that an effect of, for example, 0.5 (CI: 0.1,

0.9) can be interpreted as the effect found in this study is 0.5, with a 95% probability that the true effect in the population lies between 0.1 and 0.9. As such, a CI which is either completely positive or completely negative can be said to indicate a significant effect for an alpha of 0.05.

3.1 | Compliance with lifestyle instructions

Subjects were 100% compliant with AD instructions, while compliance with WaM and LC instructions was 79% on average.

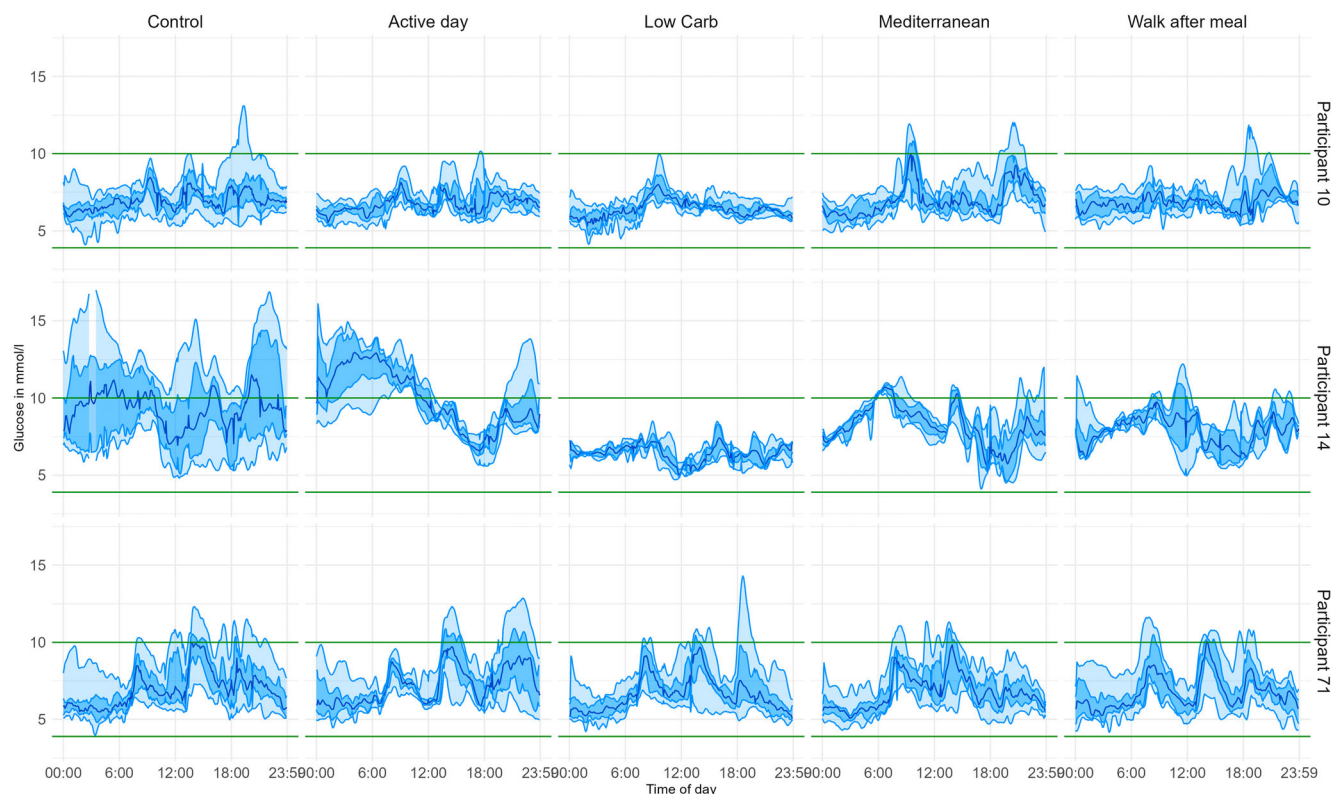


FIGURE 3 Ambulatory glucose profiles during the control periods and the four intervention phases for three participants. The target glucose range (3.9–10.0 mmol/L) is shown as two green parallel lines. The dark blue line is the median line, which is based on a rolling mean glucose, and shows whether the average glucose is within the target glucose range and how much it oscillates during the day. The darker shaded band represents the 25th–75th percentile and shows the 50% of all glucose values that are closest to the median line and their variability from day to day. The lighter shaded band represents 90% of all glucose values that are closest to the median line.

3.2 | Control periods

For the total study population, glucose levels were in range for an average of 82.4% of time and above range for 17.4% of time during the control conditions. Time below range was <1% for all study periods and was therefore excluded from analyses. Nine participants appeared to be accustomed to consuming less than 26% of calories as CHO on average (as measured by FFQ) as a means to control glycaemia even before study participation. In control conditions, their CGM metrics were clearly different from those of participants who consumed more CHO ($n = 29$) (Figure 2). In particular, according to the model, TIR was 11.3% (CI: $-6.51, 29.13$) higher, although non-significant, and CV was significantly lower (-3.86% , CI: $-5.52, -0.3$) in participants consuming <26% of calories as CHO (Table S2, intercept assumes no intervention).

3.3 | Effects of lifestyle interventions on average CGM metrics

Quite conceivably, the effects of interventions on CGM metrics were different in persons who deliberately restricted carbohydrate intake at baseline from those in participants who did not (Figure 2, Table S2). Indeed, LC clearly reduced Mean (-0.95 mmol/L, CI: $-1.13, -0.77$),

TAR-L1/L2 (-9.37% , CI: $-11.88, -6.86$, resp. -2.42% , CI: $-4.16, -0.68$) and MAGE (-1.07 mmol/L, CI: $-1.31, -0.83$) in participants consuming more than 26% of calories as CHO at baseline. However, in participants consuming less than 26% of calories as CHO at baseline, this effect was almost fully negated for Mean (0.76 mmol/L, CI: $0.37, 1.15$ higher than the >26% group) and MAGE (0.74 mmol/L, CI: $0.25, 1.23$ higher than the >26% group). In contrast, AD and WaM benefitted several CGM metrics in both groups, with for instance a decreased Mean (-0.2 , CI: $-0.38, -0.02$, resp. -0.28 , CI: $-0.46, -0.1$) and MAGE (-0.27 , CI: $-0.51, -0.03$, resp. -0.37 , CI: $-0.61, -0.13$). The Med deteriorated various metrics, such as a slight increase of TAR-L2 (2.68%, CI: $0.92, 4.44$) and CV (0.91%, CI: $0.05, 1.77$). For participants restricting CHO at baseline, several other outcomes also deteriorated (Mean: 0.69 mmol/L, CI: $0.3-1.08$; TAR L1: 5.8%, CI: $0.43, 11.17$) as well as an increase of the deterioration on CV (1.83%, CI: $0.03, 3.63$ higher than the >26% group).

3.4 | Interindividual differences in effects of lifestyle interventions on CGM metrics

Inspection of individual glucose profiles revealed apparent differences between individuals in terms of response to lifestyle intervention

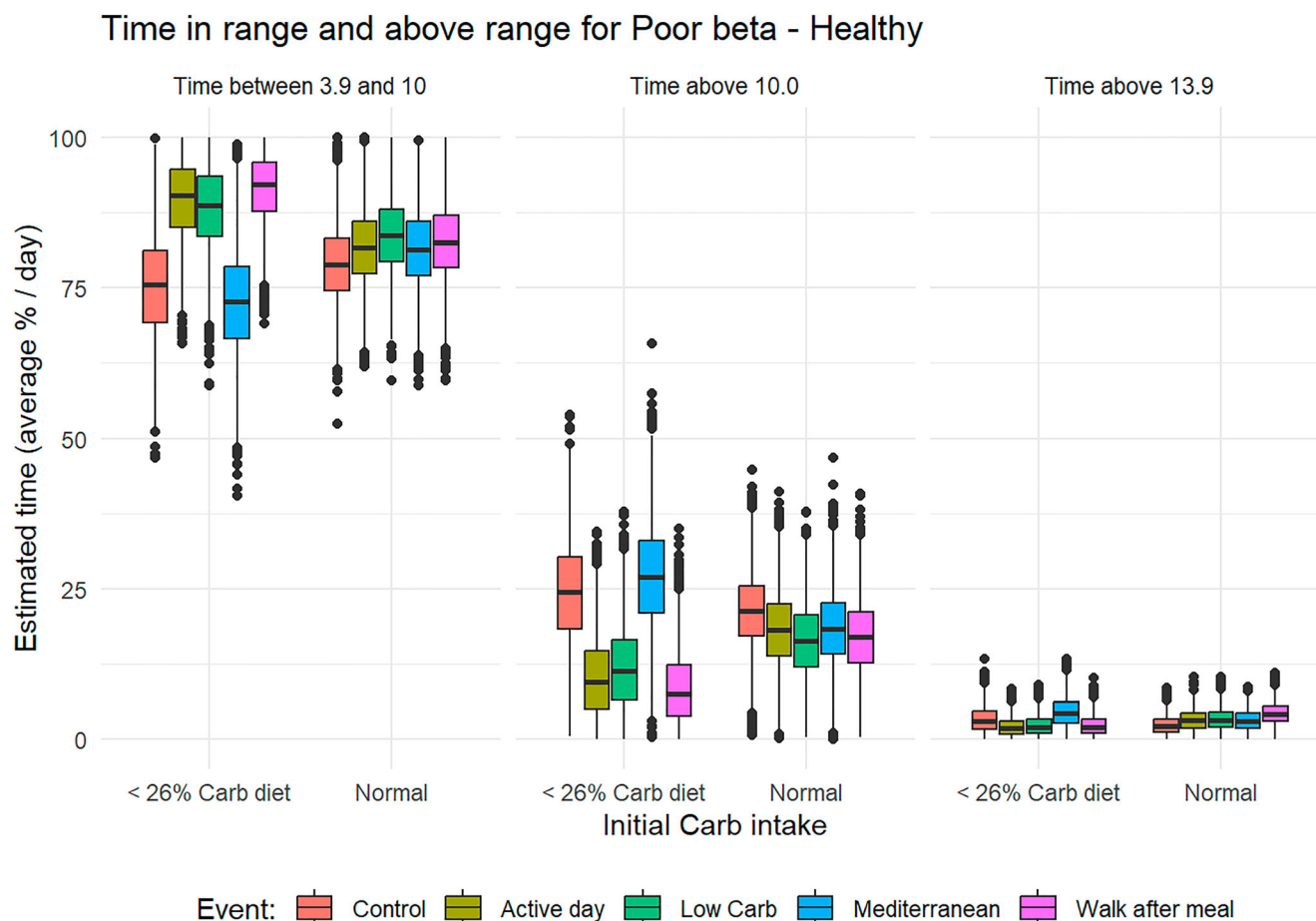


FIGURE 4 Boxplots showing estimated distributions of time in range (TIR) and time above range (TAR) in average percentage per day for control and intervention periods for participants with isolated impaired beta-cell function (PB-group). Results are presented separately for participants consuming >26% of calories as carbohydrates ($N = 8$, total of 228 days), and participants consuming <26% of calories as carbohydrates at baseline ($N = 5$, 83 days).

(Figure 3). For example, in subject 10, the mean glucose appears to improve in response to the LC, WaM, and AD interventions, while TAR seems to decline during LC and AD interventions. Glucose variability seems to be lowest during the LC intervention. In contrast, in subject 14, mean glucose, TIR, and glucose variability seem to improve in response to all but the AD intervention. In subject 71, CGM metrics appear to remain unaffected by any of the interventions.

3.5 | Post hoc analysis: Impact of diabetes phenotype on effects of lifestyle intervention

Further analysis was done post hoc to examine if interindividual differences could be explained by differences in diabetes phenotype or 'diabetype'. Figures 4–6 show the differences in TIR and TAR-L1/2 between the control and intervention periods per diabetype. During control periods, the PB-HMIR group had a lower TIR and higher TAR-L1/L2 than the PB group and PB-HIR group. Coefficients of the final models including either one of these diabetypes are listed in Table S3.

The data provides clues as to which lifestyle intervention improved CGM metrics most in each diabetype.

In people with isolated impaired BCF, AD and WaM increased TIR (and reduced TAR-L1 and TAR-L2) only in those who restricted CHO intake at baseline ($n = 5$). LC had no significant effects in this group. For participants in the PB-group with normal CHO intake at baseline, LC intervention resulted in a significantly lower mean glucose and MAGE. The Med intervention resulted in a higher CV and MAGE in those who restricted CHO at baseline and had no impact on participants with normal CHO intake at baseline.

In people with impaired BCF and hepatic IR (PB-HIR), LC, and to a lesser extent WaM, increased TIR and reduced TAR-L1 (and TAR-L2 for LC), especially in those with normal CHO intake at baseline. Additionally, LC decreased mean, CV, and MAGE. For those who restricted CHO intake at baseline ($n = 6$) beneficial effects of LC on mean and MAGE were significantly lower as compared with those with normal CHO intake at baseline. Med resulted in a significant increase in mean, MAGE, and TAR-L1 and a decrease in TIR only in those who restricted CHO intake at baseline, and an increase in TIR-L2 for those with normal CHO intake.

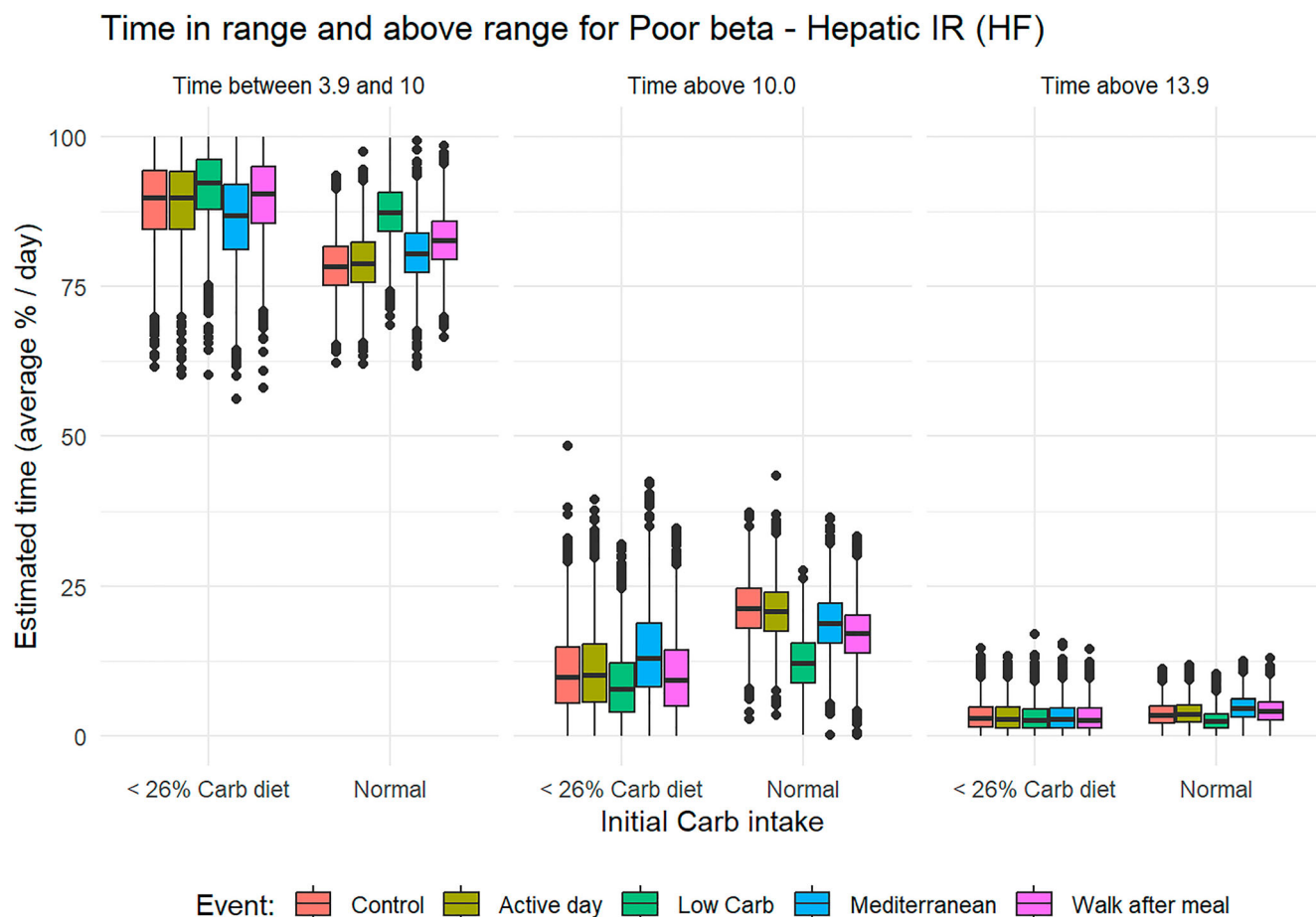


FIGURE 5 Boxplots showing estimated distributions of time in range (TIR) and time above range (TAR) in average percentage per day for control and intervention periods for participants with impaired beta-cell function and hepatic insulin resistance (PB-HIR-group). Results are presented separately for participants consuming >26% of calories as carbohydrates ($N = 19$, total of 512 days), and participants consuming <26% of calories as carbohydrate at baseline ($N = 6$, total of 220 days).

In people with impaired BCF and combined IR (PB-HMIR), the largest improvements were seen with LC and WaM, which significantly improved all CGM metrics but CV. AD resulted in a small but significant decrease in mean and MAGE, and an insignificant increase in TIR and decrease in TAR L1/L2.

4 | DISCUSSION

Within 4 days, various lifestyle interventions improved CGM metrics in patients with type 2 diabetes. The low carbohydrate intervention (LC) had the most pronounced effects, followed by statistically different but small effects for the walk after meal (WaM) and active day (AD; hourly 5-minute exercise bouts) interventions. The Mediterranean diet (Med) resulted in a small negative effect on high glucose excursions and glucose variability.

Post hoc analyses showed that, in the group with isolated poor BCF, LC intervention only had a modest effect on mean and MAGE. WaM and AD decreased TAR-L1 and increased TIR, but only in those with restricted CHO intake at baseline. In people with hepatic IR and

poor BCF, especially LC and to some extent WaM had favourable effects on CGM metrics. The Mediterranean diet had a minor negative effect only in this group, which was more pronounced in the subgroup consuming a low carbohydrate diet at baseline. In people with combined IR and poor BCF, LC and WaM, and to a lesser extent AD, resulted in favourable effects on CGM metrics. Although dedicated trials are required to confirm these findings, these preliminary findings suggest the effects of lifestyle interventions may depend on the diabetes type and habitual carbohydrate intake.

The low carbohydrate intervention lowered both glucose variability and mean glucose levels in persons with hepatic or combined IR and poor BCF. The positive effects of the LC intervention were less pronounced in the subgroup already consuming a low carbohydrate diet at baseline. A previous paper reports that a low carbohydrate energy-deficient diet ameliorates liver insulin resistance and blunts basal glucose production more than a high carbohydrate energy-deficient diet in obese subjects without type 2 diabetes.²⁹ Also, the study by Kirk et al. shows that a short-term intervention including a low carbohydrate diet is more effective in altering hepatic IR as compared with muscle IR. In our study, the effects of LC on

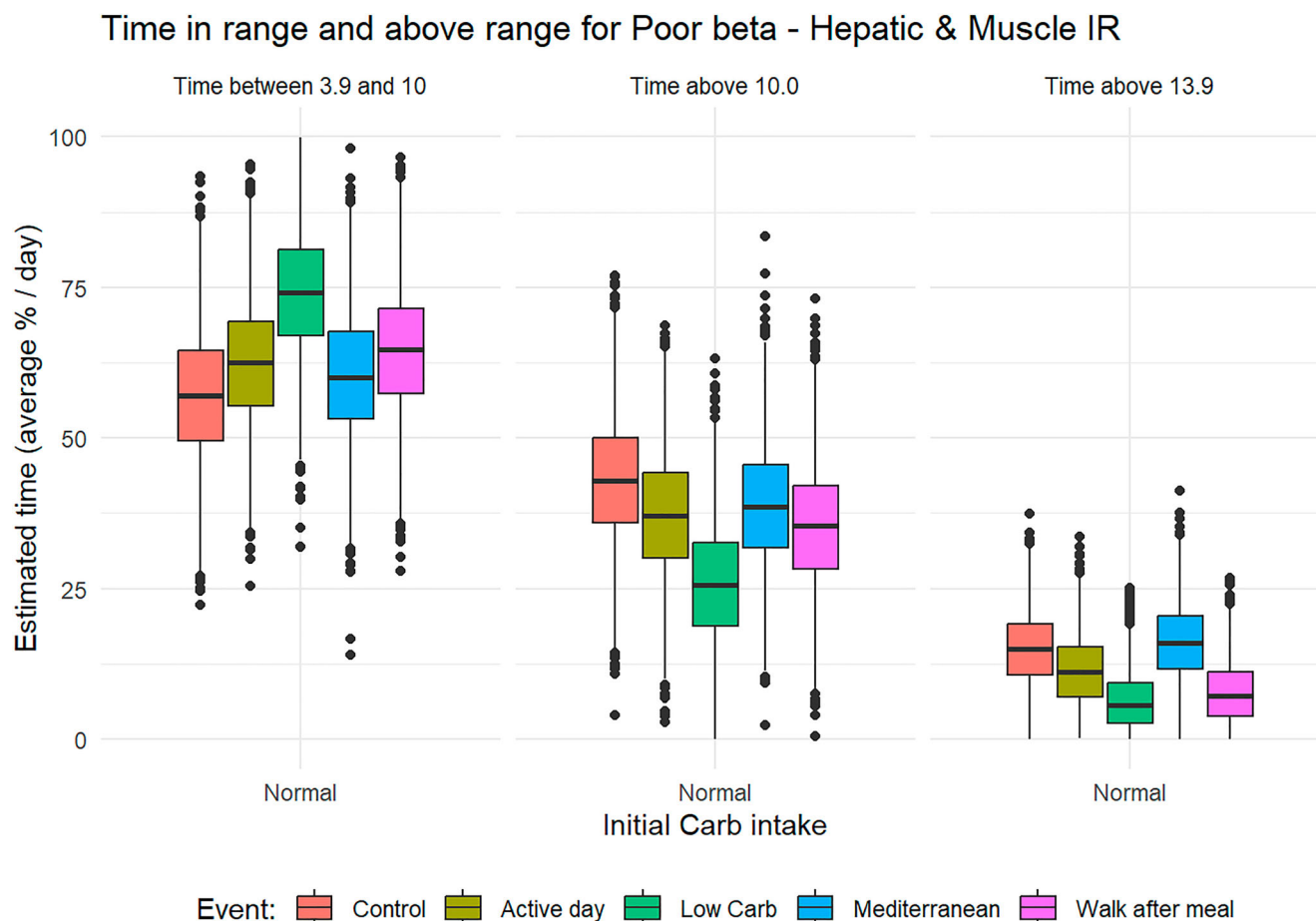


FIGURE 6 Boxplots showing estimated distributions of time in range (TIR) and time above range (TAR) in average percentage per day for control and intervention periods for participants with impaired beta-cell function and hepatic and muscle insulin resistance (PB-HMIR-group) consuming >26% of calories as carbohydrates at baseline ($N = 10$, total of 271 days).

CGM metrics were largest in the PB-HIR and PB-HMIR groups. The LC intervention was least beneficial in the group with isolated BCF, which is in line with previous research showing that the effectiveness of lifestyle interventions is dependent on the remaining capacity of the pancreas to produce insulin.³⁰

In a post hoc analysis of the CORDIOPREV-DIAB study, the Mediterranean diet appeared to improve glycaemic control more in type 2 diabetes individuals with muscle- or combined IR than in individuals with isolated liver IR.¹⁵ In our study, the Med intervention had virtually no effects on CGM metrics, except for a (almost across the board) *deterioration* in PB-HIR individuals who restricted their carbohydrate intake at baseline. However, our study investigated the (sub)acute effects of lifestyle interventions on metrics of glucose profiles, whereas the CORDIOPREV-DIAB study evaluated more traditional markers of glucose metabolism, such as HbA1c and the glucose disposition index, over a period of 2 years. Nevertheless, the lack of effect of Med on CGM metrics in our study was unexpected. Indeed, a previous meta-analysis shows that the Mediterranean diet improves glycaemic control to a similar or even larger extent than low-carbohydrate-, low glycaemic index- or high protein diets in people with type 2 diabetes.³¹ Moreover, in the long term, Mediterranean

diets are associated with a reduced risk of CVD in people with type 2 diabetes.³² We envision several possible explanations for the lack of effect of the Med intervention in our study, and even a small negative effect on TAR-L2 and CV, including the short duration of the intervention period. It could be that the positive effects of the Mediterranean diet shown in other studies are, at least partly, mediated by positive effects on the gut microbiome composition, which requires a longer-term intervention to establish.³³ Also, participants had excellent glycaemic control at baseline, and a significant part of the study population took dietary measures to manage their disease even before the study. Indeed, dietary intake during control periods may have been quite similar to the Mediterranean diet. Alternatively, it could be that the glycaemic index of foods for the Med intervention was higher compared with the usual diet of participants, as previous research shows that the effectiveness of a Med intervention on glycaemic variability may be dependent on the glycaemic index.³⁴ The preliminary finding that the Med intervention increased mean glucose, TAR and MAGE in people with the PB-HIR diabetes type who consumed <26% of calories as carbohydrate at baseline could be because the Med intervention contained more carbohydrates than this subgroup usually consumed before the study.

A meta-analysis has shown that physical exercise can reduce mean glucose and time above range, but not fasting glucose in people with type 2 diabetes.³⁵ Accordingly, in our study both the AD and WaM interventions had beneficial effects on mean glucose, TAR-L1, and MAGE. The walking after each meal intervention sorted beneficial effects in people with impaired BCF and combined IR, and to a lesser extent in people with impaired BCF and hepatic IR as compared with control periods. These preliminary observations are in line with the expectation that physical activity most effectively improves glycaemic control in people with muscle IR.¹⁸ In people with isolated poor BCF, both physical activity interventions resulted in minor negative effects on CGM metrics in persons with a normal carbohydrate intake at baseline, with a higher CV during the AD intervention and a higher TAR-L1 during the WaM intervention as compared with control periods. Interestingly, when only looking at the subgroup already consuming a low carbohydrate diet at baseline, positive effects of the AD and WaM intervention on CGM metrics were observed. It may therefore be interesting to further investigate the potential of a combination of a low carb diet with physical exercise for persons with isolated BCF in improving CGM metrics.

The interventions in this study were short term, lasting only 4 days. However, (sub)acute measures of glycaemic control are associated with long-term health outcomes in people with type 2 diabetes. For example, time in range over a couple of days CGM trace is strongly associated with the risk of macro- and microvascular complications, such as retinopathy and microalbuminuria.³⁶ Measures of glucose variability are associated with peripheral neuropathy and all-cause mortality, the latter especially in people with well-controlled glucose status.³⁷ More acute markers of glycaemic control, such as time in range, also allow for personalised treatment plans and tracking of personal goals.³⁸

It should be noted that baseline glycaemia was very well controlled in our study population. Indeed, average time in range was 82% during the control periods, while the American Diabetes Association recommends a time in range (3.9–10 mmol/L or 70–180 mg/dL) of at least 70%.¹¹ Part of the study population consumed a low carbohydrate diet before the start of the study. These baseline characteristics may well have affected our results, as the benefits of any intervention require room for improvement at baseline. This was also shown by the interaction effects between carbohydrate intake at baseline and some of the interventions. We nevertheless observed significant effects of various interventions, which probably would be even larger in a less well-controlled population. Another limitation is that the continuous glucose monitor was used in unblinded mode. Previous research has shown that the use of a continuous glucose monitor per se can drive behaviour change in people with type 2 diabetes and thereby contribute to better glycaemic control.³⁹ However, this was not apparent in our study, as there were no changes in CGM metrics over time when comparing the control periods. Additionally, as we used a repeated measures (within subject) design, we could account for behavioural change as a result of wearing a CGM by using the control periods as a reference in our models.

In conclusion, lifestyle interventions differentially impacted continuous glucose monitoring metrics in people with type 2 diabetes in the short term. The carbohydrate intake at baseline was an important determinant of the impact of any of the lifestyle interventions on CGM metrics. Furthermore, preliminary analyses suggest that the type of tissue affected by insulin resistance (i.e., liver and/or muscle) as well as the remaining beta-cell capacity may determine the direction and size of the effects of distinct lifestyle interventions, although our sample size was too small for definite conclusions.

AUTHOR CONTRIBUTIONS

Iris M. de Hoogh conducted the clinical study, researched data, and contributed to discussion. Iris M. de Hoogh and Hanno Pijl wrote the first draft of the manuscript. Tim Snel and Regina J. M. Kamstra conducted the clinical study. Tanja Krone conducted the statistical analyses. Albert A. de Graaf, Regina J. M. Kamstra, Tanja Krone, and Hanno Pijl contributed to discussion, reviewed, and edited the manuscript. All authors approved the final version of the manuscript. Iris M. de Hoogh is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

Iris M. de Hoogh, Regina J. M. Kamstra, Tanja Krone, Albert A. de Graaf, and Hanno Pijl declare no conflicts of interest. Tim Snel has a paid position at Roche Diabetes Care Nederland B.V. that markets tools related to diabetes self-management.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16654>.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available due to the data being generated as part of a public private partnership and shared intellectual property with partners, but are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study protocol was approved by the Medical Ethics Committee Brabant (NL70771.028.19). The study was performed in accordance with the Declaration of Helsinki and good clinical practice and registered at the Dutch Trial Register: NL7848. All participants provided written informed consent.

CONSENT

The authors have nothing to report.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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