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Final report for 'Reversing diabetes type 2 nutrition as medicine'

Grant number 2017-55

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Preface

This is the final report of the project 'Reversing type 2 diabetes: nutrition as medicine'. With this Ekhagastiftelsen grant, we were able to provide scientific, practiced-based evidence on the effectiveness of using nutrition and lifestyle as medicine. It showed real-life robust, durable benefits of this lifestyle group program for type 2 diabetes patients, particularly in terms of medication use, body weight and quality of life. It forms the basis to incorporate lifestyle intervention programs as these as part of regular medical practice.

We are indebted to Ekhagastiftelsen for making this work possible. In addition, we thank all participants who were willing to complete our questionnaires. We thank everyone at the Louis Bolk Institute who made this work possible. In addition, we thank the Voeding Leeft team for their cooperation.

Content

Summary

Prevalence of type 2 diabetes (T2D) is increasing rapidly and lifestyle interventions to reverse diabetes are seen as a possible solution to stop this trend. However, before these lifestyle intervention programs can be implemented into regular medical practice, scientific evidence for its effectiveness is needed.
Therefore, we evaluated the effectiveness of the multidisciplinary outpatient group-based nutrition and lifestyle intervention program 'Reverse Diabetes2 Now' (executed by Voeding Leeft) on markers of glucose regulation (haemoglobinA1c (HbA1c)) and glucose lowering medication use (GLmed). Secondary outcomes included other reported T2D biomarkers, subjective health parameters, sleep, dietary intake, physical activity and program adherence.

In 2019, we published the first results of the pilot study (doi: 10.1136/bmjnph-2018-000012*)*. We showed that after 6 months participants (n=72) had significantly improved their glucose control: they had significantly lower levels of Hb1Ac and used less medication compared to baseline. Secondary outcomes showed that participants also had significantly lower fasting glucose levels (-1.2 ±2.6mmol/L), body weight (-4.9±5.1kg), BMI (-1.70±1.69 kg/m^2) and waist circumference (-9.4±5.0cm), while no significant adverse effects on blood lipid profiles were found. Finally and most importantly, self-reported quality of life was significantly higher whilst experienced fatigue and sleep problems were significantly lower.

In 2020, we published the results of the main study including follow-up up to 24 months (doi: 10.1136/bmjnph-2020-000081). We confirmed the findings from the pilot study. Participants (n=234) still had better glucose regulation at 24months compared with baseline: 67% of the responders used less glucose-lowering medication (GLmed), and 28% ceased all GLmed. Notably, 71% of insulin users at baseline were off insulin at 24 months (n=47 of 66 insulin users). Mean HbA1c levels were similar at 24 months compared with baseline (55.6±12.8 vs. 56.3±10.5 mmol/mol, p=0.43), but more responders had HbA1c levels ≤53 mmol/mol at 24 months (53% vs 45% at baseline). Furthermore, other T2D markers all showed improvements. Triglyceride levels (−0.34±1.02 mmol/L, p=0.004), body weight (−7.0±6.8 kg, p<0.001), waist circumference (−7.9±8.2 cm, p<0.001), body mass index (−2.4±2.3 kg/m^2, p<0.001) and total cholesterol/high-density lipoprotein (HDL) ratio (−0.22±1.24, p=0.044) were lower. In addition, HDL (+0.17 ± 0.53 mmol/L, p<0.001) and low-density lipoprotein-cholesterol levels (+0.18 ± 1.06 mmol/L, p=0.040) were slightly higher. No differences were observed in fasting glucose or total cholesterol levels. Quality of life and self-reported health significantly improved.

We also investigated the impact of the program on dietary intake patterns. For this, we conducted both a cross-sectional study (n=147) as well as a prospective study in a subsample (n=22). We observed that dietary intake patterns moved towards a healthier dietary pattern and more in line with recommendations for T2D with more vegetables, less processed foods, cakes and biscuits. In terms of nutrients, we observed that participants consumed less carbohydrates and slightly more fat (only in relative terms). These results were published in December 2021 (https://doi.org/10.1111/jhn.12976).

In conclusion, with this Ekhagastiftelsen grant we were able to show real-life robust, durable benefits of this lifestyle group program for T2D patients, particularly in terms of medication use, body weight and quality of life. This has contributed to building scientific practice-based evidence needed to incorporate this lifestyle intervention program as part of regular medical practice. As of 2020, the main health insurers fund this program and currently the Dutch Health Authority is investigating whether this program should be part of basic medical care.

1 Introduction

1.1 Background

Type 2 diabetes (T2D) is a non-communicable chronic disease (NCD), originating from gene-behaviour interactions [1,2]. Unhealthy lifestyle factors, such as poor eating habits, physical inactivity, sleep deprivation and stress, contribute to the development of NCDs [3–5] and increase mortality risk [6,7]. Therefore, lifestyle modification should be a structural element of NCD treatment strategies. Although lifestyle intervention is currently mentioned in guidelines for clinical management of NCDs, current clinical practice primarily focuses drugs to relieve symptoms and prevent disease progression.

Several lifestyle intervention studies have shown promising effects in T2D patients. The DiRECT study [8,9] and the VirtaHealth trial [10,11], demonstrated a 46-64% remission rate of T2D after 2 years. However, both DiRECT (very low calorie meal replacement) and Virta (nutritional ketosis) interventions require radical changes of food consumption. Several other studies, evaluating more modest changes in one or two lifestyle components, yielded long-term (9m to 4y) benefits in T2D as well [12–14]. Most lifestyle interventions to date are primarily focussed on one or two aspects of lifestyle involved in the aetiology of T2D. However, fully effective lifestyle advice encompasses nutrition, physical activity, sleep as well as stress management [15]. In addition, sustained behaviour change requires psychological support, for example cognitive behavioural support (CBT) [16].

In 2015, the Foundation Voeding Leeft developed a multicomponent lifestyle intervention for T2D ('Reverse Diabetes2 Now' (RD2N)) to support T2D patients in their efforts to change their lifestyle to remedy their disease. RD2N is a 6-month group-program using biometric feed-back for personalized advice pertaining to the full range of lifestyle factors involved in the T2D pathogenesis. It focusses on improving skills rather than just knowledge of all relevant lifestyle components.

1.2 Aims

With this grant, we aimed to build scientific practice-based evidence so that this lifestyle intervention program to reverse type 2 diabetes could be incorporated into regular medical care.

In our studies, we evaluated the effectiveness of the multidisciplinary outpatient group-based nutrition and lifestyle intervention program 'Reverse Diabetes2 Now' measured by markers of glucose regulation (i.e. haemoglobinA1c (HbA1c) and glucose lowering medication use). Secondary outcomes included other reported T2D biomarkers, subjective health parameters, sleep, physical activity, and program adherence and dietary intake.

1.3 Hypotheses

It was hypothesized that the multidisciplinary outpatient group-based nutrition and lifestyle intervention program 'Reverse Diabetes2 Now' would lead to significant improvement of markers of glucose regulation ((i.e. haemoglobinA1c (HbA1c) and glucose lowering medication (GLmed) use) and possible other markers of cardio-metabolic health. Moreover, it was hypothesized that the multidisciplinary outpatient group-based nutrition and lifestyle intervention program 'Reverse Diabetes2 Now' would lead to significant improvement of T2D well- being and an improvement in dietary intake.

2 Material and methods

2.1 Study design

Researchers of the Louis Bolk Institute (LBI, the Netherlands) independently monitored the results of the 'Reverse Diabetes2 Now' program, which was set-up and executed by the staff of Voeding Leeft.

To evaluate the effectiveness of the 'Reverse Diabetes2 Now' program we conducted two observational evaluation studies with a pre-test post-test design. First, we conducted a *pilot* study investigating the effectiveness after 6 months. Second, we conducted a *main* study with a follow-up for up to 24 months. Thirdly, we conducted a specific study to investigate the dietary changes.

2.2 Lifestyle intervention program 'Reverse Diabetes2 Now'

'Reverse Diabetes2 Now' (RD2N) is a 6-month lifestyle intervention program to help T2D patients gain control over their disease by improving their health, nutrition and lifestyle skills. Participants were provided nutritional advice, including information to increase intake of unprocessed or minimally processed foods, low in high glycaemic carbohydrates, and corresponding a Mediterranean food pattern [17]. In addition, information was provided to enhance food and literary skills, cooking skills, manage stress, tackle mental obstacles and implement physical activity routines. Participants received 6m intensive guidance by a multidisciplinary support team, including a dietician, personal coach and nurse practitioner. To boost effectiveness, close peers of participants were also actively involved in the process [18], and participants used instant feedback measures to track their progress, e.g. measuring their own blood glucose levels before and after meals [19].

The eleven key elements of the group program 'Reverse Diabetes2 Now'.

1. *Choose unprocessed and varied food.*
2. *Be careful with sugar and starch rich foods. These can increase blood glucose levels.*
3. *Make vegetables the most important part of the meal.*
4. *Choose to eat unprocessed and natural fats.*
5. *Give your body time to rest between meals, eat a maximum of three meals a day (and no snacks).*
6. *Stop counting calories. Choose for long-term saturation by eating an adequate amount during meals.*
7. *Drink water, tea or coffee. Without additions.*
8. *Use a soft tape measure to measure your waist. Waist circumference says more than body weight.*
9. *Be physically active before the (first) meal. This way you mainly use your belly fat stock.*
10. *Plan regular moments of relaxation. Stress and tension increase blood glucose levels.*
11. *Get sufficient sleep. This helps to stabilize your blood glucose levels.*

2.3 Study population

2.3.1 Pilot study

We first conducted a pilot study of participants who completed the RD2N program between February 2015 and March 2016. Both the patient and their general practitioner (GP) provided informed consent. Patients were included using a stepped-wedge design with approximately 20 patients per group starting each month per location (a so-called convenience sample). Inclusion criteria were diagnosis of type 2 diabetes mellitus, age 18-75 years, BMI 25-41 kg/m^2, ability to speak Dutch fluently and motivation to take part in a lifestyle intervention program. Exclusion criteria were a diagnosis of type 1 diabetes, use of an insulin pump, serious co-morbidities e.g. a severe form of chronic obstructive pulmonary disease (COPD) (Gold III or IV), bariatric surgery, eating disorders, heart failure (class 2-4), or kidney failure (estimated glomerular filtration rate (eGFR)/modification of diet in renal disease (MDRD) <45 unit).

The study was approved by the Institutional Review Board of Healthcare partners Friesland. Medication use of participants was always managed by a healthcare professional (GP) in accordance with standard medical practice. The investigators had no influence on possible changes in glucose lowering medication.

2.3.2 Main study

T2D patients who started their RD2N program between January - December 2017 were enrolled in this study. Participants were included using a stepped-wedge design, with approximately 20 participants per group per location starting each month (a 'convenience sample'). Inclusion criteria for the RD2N program were T2D diagnosis, age 18-75 years, BMI 25-41kg/m^2, ability to speak Dutch fluently and motivation to take part in a lifestyle intervention program. Moreover, all participants used glucose lowering medication (GLmed) at baseline. Exclusion criteria were use of an insulin pump, serious co-morbidities, e.g. severe form of COPD (Gold III or IV), bariatric surgery, eating disorders, heart failure (class 2-4), or kidney failure (eGFR/MDRD <45 unit). Patients, as well as their physician, provided written informed consent.

The Medical Ethical Reviewing Committee of Wageningen University (NL) reviewed the study protocol and is of the opinion that it does not fall within the remit of the Dutch 'Medical Research Involving Human Subjects Act' (17 January 2019).

2.4 Outcome measures and measurements

In both the pilot and main study, data on primary outcome and most secondary outcome parameters at baseline were collected via the patients' physician. As participants became more aware of the importance of the outcome biomarkers in the course of the program, they were asked to self-report them during follow-up. Data on secondary study outcomes at baseline and all study outcomes during follow-up were collected via online questionnaires. One week prior to the initiation of the program and 1w before the final meeting at 6 months, as well as at 12, 18 and 24 months of follow-up, participants received an e-mail with a link to these questionnaires. To promote completeness of the data at 24 months, the support team actively approached participants. At 6 and 24 months of follow-up, data on the primary outcome, parameters were complemented with data from Voeding Leeft.

2.5 Dietary intake sub-studies

We conducted two dietary intake sub-studies as part of the main study: 1) a cross-sectional study in November 2018 and 2) a prospective study following participants who started their RD2N program in April-May 2019 and who were followed for 12 months. For the cross-sectional study, we invited 310 participants to complete a single web-based 24HR. As the study has stepped-wedge inclusion of participants, in November 2018 we invited one group at baseline, one group at 6 months and one group at 18 months. For the prospective study, we invited 49 participants in May 2019 at baseline. We followed these participants for up to one year.

Dietary intake data were collected using the web-based 24HR tool Compl-eat, developed by Wageningen University [20]. The online link to the 24HR tool was sent at random days to participants by email ensuring an equal distribution of all days among participants. In the 24HR tool, participants completed their foods and drinks consumed the previous day. If participants did not complete the 24HR, a reminder was sent within 2 – 6 days.
The completed web-based 24HRs were coded by Compl-eat according to the latest Dutch Dietary food composition tables (NEVO) [21]. A dietician checked the completed 24HRs for notes made by the participants and unusual portion sizes. When necessary corrections were made, no 24HR was excluded. Dietary intake was presented as mean intake of energy and nutrients (macro- and micronutrients) and main food groups.

2.6 Statistical analyses

General

Data were analysed using IBM SPSS Statistics version 26. Results were interpreted as statistically significant when $p<0.05$ (two-sided). Data were checked for missing values and impossible values. In case of missing data, data were not imputed and were analysed following an intention-to-treat principle.

Descriptive analyses were conducted to describe participant's' socio-demographic characteristics. Data were described as means ± standard deviation (SD), if they were normally distributed, or n (percentage).

Pilot and main study

Paired sample T-tests were conducted to evaluate the effects of the RD2N program on change in each measured parameter (follow-up versus baseline) and chi-square tests were used for categorical variables. Repeated measures analyses using generalized linear models (GLM) were conducted to evaluate the effects of the RD2N program on changes in each measured numerical parameter using data available at all time points.

At 24m analyses were stratified using 3 predefined subgroups: 1) HbA1c-level ≤53mmol/mol ('low HbA1c starters') or >53 mmol/mol ('high HbA1c starters'), 2) use of GLmed at baseline (categorized in two main groups: category 1 (metformin only, termed 'low GLmed') vs. category 2 and 3 (i.e. SU-derivates and/or insulin, termed 'high GLmed'); and 3) education level as proxy for socio-economic status (SES) as information on income was not available. These subgroups were predefined, as we were interested to know if any of them were more likely to respond to the intervention. People with bad metabolic control tend to respond better to (any) treatment for T2D, people with high SES are usually more amenable to lifestyle advice, and it would be useful for broad clinical implementation of the intervention to know if RD2N is particularly effective in patients using less or more medication.
Data were analysed using a per-protocol approach reporting data of those who provided data on the study outcome parameters at both baseline and 24m (='responders').

Dietary sub-studies

Nutrient intake was displayed as mean and standard deviation, adjusted for age and sex. Confounders and effect modifiers were checked using linear regression models. Confounders were age, sex, level of education and household composition. No effect modifiers were identified by using interaction terms in linear regression models. Differences in dietary intake between the three groups were tested for statistical significance with analysis of covariance (ANCOVA) adjusting for age and sex. To prevent over-adjustment the confounders level of education and household composition were not included. Fisher's least significance difference (LSD) test was used to make pairwise comparisons between the three groups (baseline, 6 and 12 months). Micronutrient intakes were also expressed per 1000 kcal, to adjust for energy intake.
Food consumption was displayed as median and interquartile range, also including non-consumers. Differences in consumption of foods between the three groups at three time points were tested using the Kruskal-Wallis test as data were highly skewed. Adjusting for confounders was therefore not possible. Dunn's post hoc method was used to make pairwise comparisons between the three groups.

3 Results

3.1 Pilot study

Of these 74 participants, 72 completed both baseline and follow-up questionnaires at 6 months on at least HbA1c and medication data. They were aged 57.4 ± 8.0 years and 56% were female (Table 3.1.1).

Table 3.1.1. Demographic characteristics of participants at baseline (n=72).

	N	**Mean ± SD or %**
Age (years)*	69	57.4 ± 8.0
Sex		
- Men	32	44%
- Women	40	56%
Education level*		
- Low	9	13%
- Middle	47	65%
- High	8	11%
- Missing	8	11%
Family structure*		
- Married/cohabiting without children (at home)	16	22%
- Married/cohabiting with children (at home)	24	33%
- Married/cohabiting with children outside home	16	22%
- Single/living alone without children (at home)	4	6%
- Single/living alone with children outside home	4	6%
- Single/living alone with children (at home)	3	4%
- Other	2	3%
- Missing	3	4%

** Data missing for age (n=3), education level (n=8) and family structure (n=3).*

Results showed that after 6 months participants significantly had lower levels of Hb1Ac and used less medication compared to baseline [22] (Table 3.1.2 and Table 3.1.3). Secondary outcomes also showed that participants had significantly lower fasting glucose levels (-1.2 ±2.6mmol/L), body weight (-4.9±5.1kg), BMI (-1.70±1.69 kg/m^2) and waist circumference (-9.4±5.0cm), while no adverse effects on blood lipid profiles were found (Table 3.1.4). Furthermore, self-reported quality of life was significantly higher whilst experienced fatigue and sleep problems were significantly lower (Table 3.1.4). These results indicate that this program provides a clinically feasible and preferable treatment option.

Table 3.1.2. Mean scores (SD) and change scores for HbA1c at baseline and at 6 months (n=72).

	N	***Baseline***	***6 months (n=72)***	***Mean difference***	***P value***
HbA1c mmol/mol	72	58.3 (12.0)	53.2 (12.5)	-5.2 (10.1)	<0.001
Subgroup analyses					
HbA1c baseline ≥ 53 mmol/mol	46	64.1 (11.3)	56.0 (14.0)	-8.1 (10.5)	<0.001
HbA1c baseline < 53 mmol/mol	26	48.1 (2.3)	48.1 (7.1)	0.04 (7.1)	0.978

Table 3.1.3. Number (and row percentage) of participants per medication class at baseline and 6 months (n=72).

		Medication class at 6 months			
Medication class at baseline	Baseline	No medication	Metformin	Metformin + SU-derivate	Metformin + SU-derivate + Insulin
No medication	7 (10%)	7	0	0	0
Metformin	13 (18%)	2	11	0	0
Metformin + SU-derivate	30 (42%)	5	17	7	1
Metformin + SU-derivate + Insulin	22 (31%)	2	8	1	11
Subtotal	*72 (100%)*	*16 (22%)*	*36 (50%)*	*8 (11%)*	*12 (17%)*

* p chi square <0.001

Table 3.1.4. Secondary outcomes: Mean scores and change scores for health parameters, experienced health, quality of life, fatigue and physical activity at baseline and at 6 months.

	N	**Baseline**	**6 months**	**Mean difference (comparing 6 months with baseline)**	**Statistical significance**
		Mean (SD)	Mean (SD)	Mean (SD)	P-value
Fasting glucose (mmol/L)	57	8.9 (2.4)	7.7 (1.9)	-1.2 (2.6)	0.001
Total cholesterol (mmol/L)	39	4.9 (1.2)	4.8 (1.3)	-0.2 (0.7)	0.235
HDL (mmol/L)	41	1.2 (0.3)	1.2 (0.3)	0.1 (0.3)	0.106
LDL (mmol/L)	41	3.0 (1.1)	2.9 (1.2)	-0.1 (0.8)	0.697
Total cholesterol/HDL ratio	34	4.3 (1.6)	4.0 (1.7)	-0.3 (1.4)	0.201
Triglycerides (mmol/L)	38	1.9 (0.9)	1.5 (0.7)	-0.4 (1.0)	0.016
Body weight (kg)	65	93.2 (14.3)	88.3 (14.9)	-4.9 (5.1)	0.000
BMI (kg/m^2)	63	31.2 (4.2)	29.5 (4.5)	-1.70 (1.69)	<0.001
Waist circumference (cm)	43	105.4 (10.2)	96.1 (9.6)	-9.4 (5.0)	<0.001
Health	53	6.7 (1.5)	7.6 (1.5)	0.9 (1.8)	0.001
Quality of life	53	7.0 (1.5)	7.5 (1.6)	0.5 (1.6)	0.022
Fatigue (CIS-score)	51	58.7 (21.5)	52.4 (21.1)	-6.3 (18.0)	0.016
Sleep (bad sleep)	54	3.1 (2.0)	2.5(1.7)	-0.7 (1.5)	0.002
Moderate physical activity	54	3.6 (1.2)	4.0 (1.1)	0.4 (1.3)	0.013
Intensive physical activity	54	1.9 (1.3)	2.1 (1.4)	0.2 (1.5)	0.459

3.2 Main study

Of the 428 participants who started with this study, 234 participants provided information on GLmed and HbA1c ('responders') after 24 months (Table 3.2.1). The baseline characteristics of the responders (n=234) were similar to those of all participants who started the program (n=438) (Table 3.2.1). Due to missing or invalid answers, data on secondary outcomes at 24m are presented for fewer participants, varying from 111 to 195 of the 438 participants (25-45%) per outcome measure. The responders' age ranged from 22-75 years, and was 61.3 ± 8.5 years on average (Table 3.2.1). Just over half the responders were men (53%) and 54% had low or middle education.

Table 3.2.1. Demographic characteristics at baseline of all participants (n=438) and of those who provided data on HbA1c and GLmed use at both baseline and 24 months ('responders', n=234)

	All (n=438)		Responders (n=234)	
	N	**Mean (SD) or %**	**N**	**Mean (SD) or %**
Age (years)*	438	60.6 (8.9)	234	61.3 (8.5)
Sex				
- Men	241	55%	123	53%
- Women	193	44%	109	47%
- Missing	4	1%	2	1%
Education level*[a]				
- Low	119	27%	57	24%
- Middle	129	29%	69	30%
- High	184	42%	106	45%
- Missing	6	1%	2	1%
Family structure*[b]				
- Single – no children living at home	74	17%	38	16%
- Married/cohabiting without children at home	223	51%	126	54%
- Single/Married/cohabiting with children at home	134	31%	68	29%
- Missing	7	2%	2	1%
Time since diagnosis of type 2 diabetes (in years)	328	8.8 (5.8)	191	8.7 (5.9)

**missing for some responders*

[a] Low level of education (no education, elementary school and pre-vocational education), middle level of education (higher general secondary education, pre-university education and secondary vocational education), high level of education (higher professional education and university education).

[b] Married/living together without (dwelling) children (married/living together without children and married/living together without dwelling children), single without (dwelling) children (single without children and single without dwelling children).

67% of the responders used less GLmed, 28% ceased all GLmed (Figure 3.2.1 and Table 3.2.2). Notably, 71% of insulin-users at baseline (n=47 of n=66 insulin users) were off insulin at 24m. Mean HbA1c-levels were similar at 24 months compared with baseline (55.6 ± 12.8 vs. 56.3 ± 10.5mmol/mol, p=0.43), but more responders had HbA1c-levels <53 mmol/mol at 24m (53% vs. 45% at baseline). Furthermore, triglyceride levels (-0.34 ± 1.02mmol/L, p=0.004), body weight (-7.1 ± 6.8kg, p<0.001), waist circumference (-7.9 ± 8.2cm, p <0.001), BMI (-2.4 ± 2.3kg/m^2, p<0.001) and total cholesterol/HDL-ratio (-0.22 ±1.24 , p=0.044) were lower, whilst

HDL (+0.17 ± 0.53mmol/L, p<0.001) and LDL-cholesterol levels (+0.18 ± 1.06 mmol/L, p=0.040) were slightly higher. No differences were observed in fasting glucose or total-cholesterol levels. Quality of life and self-reported health significantly improved.

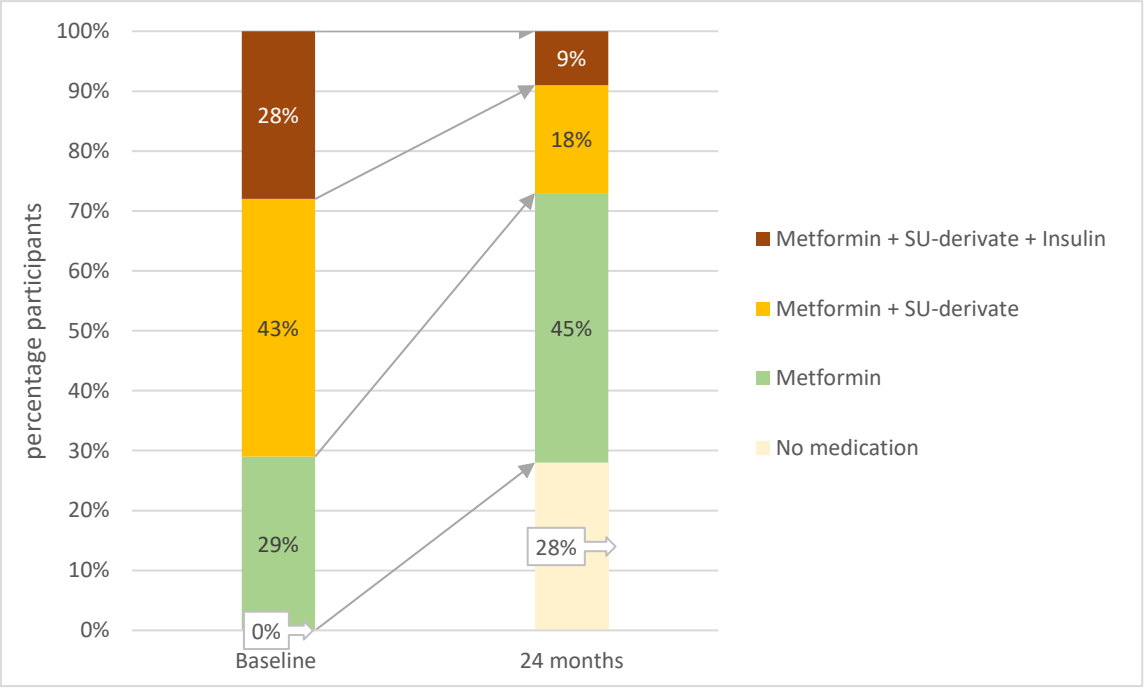

Figure 3.2.1. Percentage of responders in various GLmed categories at baseline and at 24 months (n=234)

Table 3.2.2. Secondary outcomes: mean scores and changes of health parameters, self-perceived health, quality of life and fatigue at baseline and 24 months

	N (used for paired t-test)	**Baseline**	**24 months**	**Mean difference (24m vs. baseline)**	**Paired sample t-test**	**Repeated measures analysis(GLM)**
		Mean (SD)	Mean (SD)	Mean (SD)	P-value	P-value
Fasting glucose (mmol/L)	151	8.7 (2.1)	8.8 (2.5)	0.12 (2.53)	0.575	0.126
Total cholesterol (mmol/L)	136	4.6 (1.2)	4.8 (1.2)	0.20 (1.23)	0.057	0.247
HDL (mmol/L)	139	1.3 (0.4)	1.4 (0.5)	0.17 (0.53)	<0.001	0.169
LDL (mmol/L)	155	2.6 (1.0)	2.8 (1.1)	0.18 (1.06)	0.040	0.331
Total cholesterol/HDL ratio	126	3.9 (1.2)	3.7 (1.3)	-0.22 (1.24)	0.044	0.156
Triglycerides (mmol/L)	134	2.1 (1.2)	1.7 (1.1)	-0.34 (1.02)	<0.001	0.004
Body weight (kg)	179	94.1 (15.6)	87.0 (14.7)	-7.01 (6.84)	<0.001	<0.0001
BMI (kg/m^2)	179	31.4 (4.3)	29.0 (4.0)	-2.36 (2.28)	<0.001	<0.0001
Waist circumference (cm)	111	110.4 (12.2)	102.5 (11.1)	-7.87 (8.24)	<0.001	<0.0001
Subjective health parameters						
Health (score 1-10)	195	6.9 (1.3)	7.3 (1.6)	0.42 (1.49)	<0.001	<0.0001
Quality of life (score 1-10)	195	7.4 (1.2)	7.6 (1.4)	0.28 (1.33)	0.004	0.001
Fatigue (CIS-score 20-140)	195	64.3 (23.4)	54.8 (24.4)	-9.53 (20.72)	<0.001	<0.0001

3.3 Dietary intake sub-studies

For the cross-sectional study, 310 participants received an invitation to complete the web-based 24HR. 147 participants (47% of the 310 participants) completed the 24HR. The baseline group included 37 participants (74% response rate), 58 participants at 6 months responded (53%) and 52 participants at 12 months (47%). No major differences in socio-demographic characteristics were found between the three different groups, only that group at baseline was significantly younger than the group at 12 months (p= 0.015) (Table 3.3.1). In all groups, more men than women participated, and most of the participants lived together without (resident) children.

Table 3.3.1. Socio-demographics of groups at baseline, 6 and 12 months of the group program 'Reverse Diabetes2 Now' presented as mean (SD) or n(%)

Socio-demographics	**Group at baseline (n=37)** [a]	**Group at 6 months (n=58)**	**Group at 12 months (n=52)** [b]
Age (years)	58.5 (7.1)	62.4 (8.0)	63.5 (8.3)
Sex: Men n (%)	19 (53%)	39 (67%)	31 (60%)
Level of education [c], n (%)			
Low	10 (27.8%)	11 (19.0%)	9 (17.6%)
Middle	13 (36.1%)	23 (39.7%)	19 (37.3%)
High	13 (36.1%)	24 (41.3%)	23 (45.1%)
Household composition [d], n (%)			
Single without (dwelling) children	11 (30.6%)	12 (20.7%)	8 (15.4%)
Married/ living together without (dwelling) children	15 (41.7%)	34 (58.6%)	32 (61.5%)
Single/Married/ living together with dwelling children	10 (27.8%)	11 (19.0%)	12 (23.1%)
Other	0 (0%)	1 (1.7%)	0 (0%)

[a] Data missing in the group at baseline for age (n= 5), sex (n=1), level of education (n=1) and household composition (n=1).
[b] Data missing in the group at 12 months for level of education (n=1).
[c] Low level of education (no education, elementary school and pre-vocational education), middle level of education (higher general secondary education, pre-university education and secondary vocational education), high level of education (higher professional education and university education).
[d] Married/living together without (dwelling) children (married/living together without children and married/living together without dwelling children), single without (dwelling) children (single without children and single without dwelling children).

Table 3.3.2 describes T2D related factors of the participants of the three groups. Only HDL-cholesterol levels at baseline were significantly lower in the group at 6 months compared to the group at 12 months (p= 0.017). For participants at 6 and 12 months, BMI and waist circumference were significantly lower. HbA1c levels were lower in the group at 6 months. For total cholesterol and LDL-cholesterol, no differences were found in the groups at 6 and 12 months. HDL-cholesterol was significantly higher the group at 6 months. For the group at 12 months no further differences were found over time.

Table 3.3.2. T2D related factors of groups at baseline, 6 and 12 months of the group program 'Reverse Diabetes2 Now' for the cross-sectional dietary sub-study [a]

Characteristics	Group at baseline (n=37)	Group at 6 months (n=58) [b]	Group at 12 months (n=52) [c]
Anthropometry			
Body weight (kg)			
At baseline	96.8 (15.4)	97.2 (17.2)	94.9 (13.4)
At 6 months		89.2 (16.6) [d]	87.8 (11.2) [d]
At 12 months			85.6 (12.1) [d]
BMI (kg/m^2)			
At baseline	32.2 (3.8)	32.2 (5.6)	32.1 (4.4)
At 6 months		29.7 (5.5) [d]	29.2 (3.6) [d]
At 12 months			29.2 (3.8) [d]
Waist circumference (cm)			
At baseline	109.4 (10.1)	111.5 (11.3)	111.8 (11.1)
At 6 months		102.0 (11.0) [d]	101.3 (8.7) [d]
At 12 months			101.3 (10.9) [d]
T2D parameters			
HbA1C (mmol/mol)			
At baseline	61.0 (12.6)	55.4 (10.5)	53.6 (10.4)
At 6 months		48.5 (10.3) [d]	51.6 (11.3)
At 12 months			50.6 (10.0)
Diabetes medications			
No medication, n (%)			
At baseline	0 (0%)	0 (0.0%)	0 (0.0%)
At 6 months		8 (14.5%)	11 (22.4%)
At 12 months			16 (37.2%)
Metformin, n (%)			
At baseline	14 (37.8%)	26 (44.8%)	16 (32.0%)
At 6 months		43 (78.2%)	34 (69.4%)
At 12 months			22 (51.2%)
SU-derivate (+ Metformin), n (%)			
At baseline	9 (24.3%)	17 (29.3%)	21 (42.0%)
At 6 months		0 (0.0%)	2 (4.1%)
At 12 months			2 (4.7%)
Insulin (+ SU-derivate and Metformin), n (%)			
At baseline	12 (32.4%)	15 (25.9%)	13 (26.0%)
At 6 months		4 (7.3%)	2 (4.1%)
At 12 months			3 (7.0%)
Lipids			
Total cholesterol (mmol/L)			
At baseline	4.7 (1.0)	4.5 (1.1)	4.7 (1.0)
At 6 months		4.6 (1.4)	4.4 (0.9)
At 12 months			4.9 (1.5)
LDL-cholesterol (mmol/L)			
At baseline	2.7 (0.8)	2.6 (0.9)	2.4 (0.8)
At 6 months		2.8 (1.2)	2.5 (0.8)
At 12 months			2.6 (1.1)
HDL- cholesterol (mmol/L)			
At baseline	1.2 (0.3)	1.1 (0.2)	1.3 (0.6)
At 6 months		1.3 (0.3) [d]	1.4 (0.3)
At 12 months			1.4 (0.4)
Cholesterol/HDL ratio (mmol/L)			
At baseline	4.2 (1.2)	4.3 (1.2)	3.9 (1.2)
At 6 months		3.9 (1.2) [d]	3.5 (1.0)
At 12 months			3.8 (1.4)
Triglycerides (mmol/L)			
At baseline	2.1 (0.9)	2.2 (1.2)	2.3 (1.6)
At 6 months		1.6 (1.0) [d]	1.6 (0.9)
At 12 months			1.8 (1.5)

N.A., Not available, BMI, Body Mass Index

[a] Data are mean (SD) or n (%).

[b] Data missing for the group at 6 months vary between 0 and 16.

[c] Data missing for the group at 12 months vary between 1 and 28.

[d] Significant differences within group compared to values at baseline ($p<0.05$).

Nutrient intake

The mean energy intake was lower for the group at 6 months (1297±515 kcal/d) and for the group at 12 months (1387±517 kcal/d) than for the group at baseline (1724±525 kcal/d) (Table 3.3.3). The absolute intake of carbohydrates nearly halved for the groups at 6 and 12 months (64±44 and 76±44 g/d, respectively) compared to the group at baseline (143±45 g/d). The absolute intake of total fat and saturated fat did not differ between the three groups. For relative intakes, slightly different findings were observed. The percentage of energy of total fat was higher for the group at 6 months (51.8±9.9E%/d) and the group at 12 months (51.7±10.0 E%/d) compared to the group at baseline (41.8±10.1 E%/d). In addition, for saturated fat, the percentage of energy was higher for the groups at 6 and 12 months (21.2±5.3 and 21.9±5.3 E%/d, respectively) than for group at baseline (16.4±5.4 E%/d). The absolute iodine intake was lower for groups at 6 and 12 months (97±60 and 101±60 mg/d, respectively) compared to the group at baseline (141±61 mg/d). No differences were found for other micronutrients (Table 3.3.3).

Food consumption

Fruit consumption was lower in the group at 12 months (median 0.0 [IQR 100.0] g/d) compared to the group at baseline (median 114.0 [IQR 162.5] g/d), but no significant differences were found between the group at baseline and the group at 6 months (Table 4). In contrast, vegetable consumption nearly doubled from median 123.1 [184.6] g/d in the group at baseline to median 270.0 [IQR 285.4] and median 240.0 [IQR 252.9] g/d in the groups at 6 and 12 months, respectively. Consumption of potatoes was low at baseline (0.0 [IQR 25.0] g/d) and dropped even further.

Consumption of bread, crisps, spreads and sauces almost diminished over time (Table 3.3.4). The consumption of cake and cookies, and pasta, rice and tortillas were lower in the groups at 6 and 12 months compared to the group at baseline. In contrast, consumption of crackers and crispbread was higher in the groups at 6 and 12 months compared to the group at baseline. The consumption of milk and milk products differed for several products between the three groups. Consumption of low-fat yoghurt, (semi) skimmed milk and cheese were higher at the group at baseline compared to the groups at 6 and 12 months where consumption of full-fat yoghurt was higher.

The consumption of artificially sweetened soft drinks was lower in the groups at 6 and 12 months (median 0.0 [IQR 0.0] and median 0.0 [IQR 0.0] g/d, respectively) compared to the group at baseline (median 0.0 [IQR 185.0] g/d).

Table 3.3.3. Nutrient intake of the cross-sectional dietary sub-study of groups at baseline, 6m and 12m of the group program 'Reverse Diabetes2 Now' adjusted for age and sex [a]

Nutrients	Group at baseline (n=32) [b]	Group at 6m (n=58)	Group at 12m (n=52)	p-value between groups*	p-value baseline vs. 6m**	p-value baseline vs. 12 m**	p-value 6m vs. 12m**
Total energy (kcal/d)	1724 (525)	1297 (515)	1387 (517)	**0.001**	**<0.001**	**0.005**	0.362
Protein (E%/d)	18.8 (5.6)	21.5 (5.5)	20.6 (5.6)	0.097	0.031	0.161	0.393
Protein (g/d)	79 (27)	66 (26)	69 (27)	0.069	0.022	0.101	0.462
Total fat (E%/d)	41.8 (10.1)	51.8 (9.9)	51.7 (10.0)	**<0.001**	**<0.001**	**<0.001**	0.932
Total fat (g/d)	85(39)	78(38)	82 (38)	0.707	0.418	0.704	0.622
Saturated fat (E%/d)	16.4 (5.4)	21.2 (5.3)	21.9 (5.3)	**<0.001**	**<0.001**	**<0.001**	0.535
Saturated fat (g/d)	32 (15)	31 (15)	34 (15)	0.647	0.787	0.612	0.355
Monounsaturated fat (E%/d)	14.6 (5.3)	17.3 (5.2)	16.8 (5.2)	0.056	0.018	0.063	0.583
Monounsaturated fat (g/d)	30(16)	26 (16)	27 (16)	0.528	0.268	0.376	0.816
Polyunsaturated fat (E%/d)	7.5 (3.7)	8.6 (3.7)	8.3 (3.7)	0.430	0.198	0.343	0.710
Polyunsaturated fat (g/d)	15 (9)	13 (9)	13 (9)	0.482	0.282	0.266	0.939
Trans fat (E%/d) [c]	0.5 (0.4)	0.6 (0.4)	0.7 (0.4)	0.091	0.142	0.029	0.357
Trans fat (g) [c]	0.9 (0.6)	0.9 (0.6)	1.0 (0.6)	0.501	0.729	0.526	0.729
EPA and DHA (E%/d) [c]	0.08 (0.49)	0.27 (0.48)	0.13 (0.48)	0.133	0.065	0.555	0.144
EPA and DHA (mg/d) [c]	115 (992)	459 (973)	201 (978)	0.216	0.089	0.434	0.290
Carbohydrates (E%/d)	35.4 (9.7)	21.1 (9.5)	22.7 (9.6)	**<0.001**	**<0.001**	**<0.001**	0.372
Carbohydrates (g/d)	143 (45)	64 (44)	76 (44)	**<0.001**	**<0.001**	**<0.001**	0.156
Dietary fibre (E%/d)	2.1 (1.1)	2.5 (1.1)	2.6 (1.1)	0.155	0.162	0.055	0.501
Dietary fibre (g/d)	19 (8)	16 (8)	18 (8)	0.274	0.136	0.614	0.253
Alcohol (E%/d) [d]	1.6 (5.8)	2.7 (5.7)	2.1 (5.8)	0.447	0.208	0.380	0.691
Alcohol (g/d) [d]	4 (13)	6 (13)	5 (13)	0.527	0.263	0.243	0.741
Sodium (mg/d)	2223 (988)	1741 (970)	1803 (978)	0.075	0.028	0.061	0.741
Potassium (mg/d)	2855 (968)	2652 (950)	2772 (954)	0.608	0.343	0.704	0.511
Iodine (µg/d)	141 (61)	97 (60)	101 (60)	**0.004**	**0.002**	**0.005**	0.742
Calcium (mg/d)	829 (360)	810 (354)	823 (355)	0.968	0.813	0.936	0.856
Total iron (mg/d)	10.2 (3.5)	8.5 (3.4)	9.1 (3.4)	0.087	0.027	0.154	0.376
Folate (µg/d) [c]	239 (205)	246 (201)	266 (202)	0.980	0.843	0.911	0.921
Vitamin B12 (µg/d) [c]	4.5 (4.6)	4.4 (4.5)	4.4 (4.5)	0.475	0.235	0.574	0.473
Vitamin C (mg/d) [c]	93 (102)	94 (100)	101 (101)	0.903	0.741	0.983	0.741

E%, percentage of energy

[a] Data are estimated marginal means intakes per day adjusted for age and sex (SD).

[b] Sample size reduced by 5 cases due to missing data of age.

[c] Data were log-transformed to get normality for statistical analyses but means and S.D. are presented non-transformed.

[d] Comparisons between groups were performed using the non-parametric Kruskal-Wallis test, post hoc comparisons were performed using Dunn's post hoc test, therefore p-values were not adjusted for age and sex.

* Comparisons between groups were performed using ANCOVA adjusted for age and sex.

** Post-hoc comparisons were performed using LSD post hoc test.

Table 3.3.4 Consumption of foods of the cross-sectional dietary sub-study of groups at baseline, 6m and 12m of the group program 'Reverse Diabetes2 Now' ¤

Food groups (in g/d)	Group at baseline (n=37)	Group at 6m (n=58)	Group at 12m (n=52)	p-value between groups*	p-value baseline vs. 6m**	p-value baseline vs. 12m**	p-value 6m vs. 12m**
Fruit	114.0 [162.5]	56.3 [127.9]	0 [100.0]	**0.027**	0.950	**0.029**	**0.017**
Vegetables	123.1 [184.6]	270.0 [285.4]	240.0 [252.9]	**0.001**	**<0.001**	**0.002**	0.588
Potatoes	0.0 [25.0]	0.0 [0.0]	0.0 [0.0]	**0.001**	**<0.001**	0.114	0.023
Legumes	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.765	0.483	0.802	0.624
Nuts and seeds	0.0 [3.3]	13.8 [25.0]	0.0 [25.0]	0.068	0.021	0.170	0.314
Eggs	8.8 [100.0]	0.0 [50.0]	0.0 [50.0]	0.282	0.124	0.213	0.771
Crackers and crispbread	0.0 [5.0]	0.0 [24.0]	8.0 [20.0]	**0.029**	**0.025**	**0.013**	0.743
Bread	50.0 [105.0]	0.0 [0.0]	0.0 [0.0]	**<0.001**	**<0.001**	**<0.001**	0.679
Low carb bread	0.0 [35.0]	0.0 [35.0]	0.0 [70.0]	0.715	0.986	0.504	0.464
Cakes and sweet biscuits	8.0 [28.5]	0.0 [0.0]	0.0 [0.0]	**<0.001**	**<0.001**	**<0.001**	0.464
Breakfast cereals	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.076	0.111	0.728	0.032
Pasta, rice, tortillas	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	**0.002**	**0.001**	**0.008**	0.443
Semi-skimmed and skimmed milk	0.0 [15.0]	0.0 [0.0]	0.0 [0.0]	**<0.001**	**<0.001**	**<0.001**	0.754
Whole milk	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.162	0.415	0.709	0.187
Low fat yoghurt	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	**0.004**	**0.035**	**0.001**	0.165
Full fat yoghurt	0.0 [0.0]	150.0 [132.5]	150.0 [287.5]	**<0.001**	**<0.001**	**<0.001**	0.947
Cream	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.162	0.304	0.057	0.312
Cheese ≤ 30+	0.0 [20.0]	0.0 [0.0]	0.0 [0.0]	**0.010**	**0.006**	**0.009**	0.918
Cheese > 30+	0.0 [40.0]	22.0 [44.0]	0.0 [40.0]	0.236	0.124	0.738	0.188
Coffee and tea	750.0 [525.0]	662.5 [500.0]	787.5 [720.0]	0.050	0.550	0.121	0.016
Fruit juice	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.308	0.241	0.135	0.694
Sugar sweetened soft drinks	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.186	0.162	0.907	0.095
Artificially sweetened soft drinks	0.0 [185.0]	0.0 [0.0]	0.0 [0.0]	**<0.001**	**<0.001**	**<0.001**	0.541
Alcoholic beverages	0.0 [0.0]	0.0 [0.6]	0.0 [0.0]	0.313	0.129	0.310	0.596
Soup	0.0 [7.6]	0.0 [250.0]	0.0 [250.0]	0.051	0.016	0.265	0.162
Crisps	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	**<0.001**	**<0.001**	**<0.001**	0.674
Chocolate, bonbons	0.0 [0.0]	0.0 [0.0]	0.0 [7.0]	0.383	0.899	0.303	0.193
Butter	0.0 [12.0]	0.0 [10.5]	0.0 [12.0]	0.893	0.803	0.861	0.637
Margarine and cooking fats	0.0 [2.8]	0.0 [3.8]	0.0 [2.0]	0.334	0.688	0.366	0.144
Spreads	0.0 [9.0]	0.0 [0.0]	0.0 [0.0]	**<0.001**	**<0.001**	**<0.001**	0.520
Oil	0.0 [6.6]	0.0 [6.1]	0.0 [5.8]	0.824	0.789	0.542	0.696
Sauce	0.0 [18.3]	0.0 [0.0]	0.0 [2.7]	**0.005**	**0.001**	0.092	0.088
Oily fish	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.440	0.450	0.704	0.208
White fish	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.497	0.240	0.546	0.539

¤ Data are median intake per day [interquartile range (IQR)].
* Comparisons between groups were performed using the non-parametric Kruskal-Wallis test ** Post hoc comparisons were performed using Dunn's post hoc test

Prospective study

For the prospective study, of the 49 participants who were invited, 42 participants (86%) completed 24HR at baseline of whom the majority (n=35 out of 42) reported dietary intake over 2 or 3 days. At 6 months, 23 participants completed (55% of 42) with at least one 24HR.

Participants were invited again at 12 months to complete a final round of 24HR; this was slightly delayed due to the COVID-19 pandemic (May 2020). Of the 23 participants, 22 participants completed 24HR at 6 months also completed 24HR at 12-14 months. As the number of participants at 6 and 12 months was very limited, we only describe the data and we did not perform any statistical testing.

Total energy intake was lower with 1469 ± 607 kcal/d at 6 months and 1529 ± 496kcal/d at 12-14 months compared with baseline (1681 ± 505 kcal/d) (Appendix Table 1). The percent contribution to total energy intake of carbohydrates was lower at 6 months (23.7 ± 12.9 E%) and 12-14 months (28.8 ±11.8 E%) compared with baseline (35.0 ± 12.2 E%). When looking at absolute intake of macronutrients (in g/d), intake of carbohydrates went down (from 142±68 g/d at baseline to 76.8±34.9 g/d at 6 months and 103.4±51.3g/d) at 12-14 months , protein remained fairly similar comparing baseline (79.1 ± 22.9g/d) with 12-14m (75.1±25.3g/d), and fat intake went up a little (41.4±10.0 baseline, 50.4±11.9g/d at 6m and 46.3±11.4g/d at 12-14m), which was mostly due to an increase in monounsaturated fat intake (in g/d) and slightly from saturated fat intake.

Of the micronutrients, iodine intake was lower at 6 months (113.4±61.7 µg/d) and 12-14months (121.4±89.6 µg/d) compared with baseline (158.6 ±52.6 µg/d). Intakes of vitamin B12, calcium, vitamin C, and folate were somewhat higher at 6 and 12-14 months compared with baseline.

In terms of food consumption, we observed that consumption of crackers and crispbread increased and consumption of bread, cakes and biscuits decreased (Table 3.3.6). Consumption of vegetables, dairy products, coffee and tea, water, meat and meat products, cheese increased somewhat whereas consumption of fruit, potatoes, sugar and confectionary, fats and oils decreased somewhat. Consumption of the following food groups was nearly zero and remained largely not consumed: legumes, breakfast cereals, pasta- rice -and tortillas, margarine and cooking fats, oil, fish, soya and vegetarian products, fruit and vegetable juices, soft drinks and lemonade, and alcoholic drinks

Table 3.3.5 Average nutrient intake of prospective sub-study on dietary changes in lifestyle intervention program 'Reverse Diabetes 2 Now' at baseline, 6 months and 12-14 months

	Baseline	**(N=42)**	**6 months**	**(N=23)**	**12-14 months**	**(N=22)**
Nutrients	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Total energy (kcal/d)	1681	505	1469	607	1529	496
Total energy (MJ/d)	7.0	2.1	6.1	2.5	6.4	2.1
Protein (E%/d)	19.7	4.1	22.1	4.2	20.8	4.4
Protein (g/d)	79.1	22.9	77.4	32.0	75.1	25.3
Total fat (E%/d)	41.4	10.0	50.4	11.9	46.3	11.4
Total fat (g/d)	80.6	31.2	87.5	42.4	82.8	34.6
Saturated fat (E%/d)	16.8	23.3	20.8	26.0	19.8	28.7
Saturated fat (g/d)	31.4	13.1	33.9	17.5	33.7	15.8
Monounsaturated fat (E%/d)	14.4	20.3	18.6	24.3	15.9	23.2
Monounsaturated fat (g/d)	26.8	11.4	30.4	16.4	27.0	12.8
Polyunsaturated fat (E%/d)	7.8	12.7	8.7	12.8	7.9	13.3
Polyunsaturated fat (g/d)	14.6	7.1	14.2	8.6	13.5	7.3
Trans fat (E%/d) [c]	0.53	1.09	0.59	1.07	0.54	1.08
Trans fat (g/d) [c]	1.0	0.6	1.0	0.7	0.9	0.6
EPA and DHA (E%/d) [c]	0.18	1.07	0.24	0.86	0.14	0.70
EPA and DHA (mg/d) [c]	0.34	0.60	0.39	0.58	0.24	0.39
Carbohydrates (E%/d)	35.0	12.2	23.7	12.9	28.8	11.8
Carbohydrates (g/d)	142.3	67.5	76.8	34.9	103.4	51.3
Dietary fibre (E%/d)	2.2	0.8	2.4	1.0	2.3	0.7
Dietary fibre (g/d)	18.2	7.1	16.6	7.6	17.9	6.5
Alcohol (E%/d) [d]	1.2	2.9	1.1	3.9	1.4	3.8
Alcohol (g/d) [d]	3.8	10.2	3.6	13.6	4.1	12.3
Sodium (mg/d)	2071.2	799.6	1768.9	1022.9	1907.1	709.2
Potassium (mg/d)	2879.8	830.0	2774.5	1017.4	2850.5	1022.8
Iodine (µg/d)	158.6	52.6	113.4	61.7	121.4	89.6
Calcium (mg/d)	873.5	340.6	899.1	512.2	919.9	419.8
Total iron (mg/d)	9.8	3.0	9.7	3.5	9.8	3.1
Folate (µg/d) [c]	229.7	78.8	267.1	130.2	267.5	120.1
Vitamin B12 (µg/d) [c]	4.2	2.4	6.2	5.5	4.3	2.9
Vitamin C (mg/d) [c]	67.0	38.8	79.1	55.8	86.8	73.8

Table 3.3.6 Food consumption, including non-consumers (presented as median (IQR) as data not normally distributed of prospective sub-study on dietary changes in lifestyle intervention program 'Reverse Diabetes 2 Now' at baseline, 6 months and 12-14 months

	Baseline (n=42)		**6 months (n=23)**		**12-14 months (n=22)**	
Food groups (in g/d)	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Fruit	101.0	59.9	45.0	100.0	49.2	102.8
Vegetables	89.4	72.4	145.1	102.5	101.5	88.8
Potatoes	42.8	150.0	0	96	0.0	70.0
Legumes	0.0	0.0	0.0	0.0	0.0	0.0
Nuts and seeds	18.5	29.0	13.0	25.0	20.9	33.3
Eggs	50.0	60.7	50.0	83.5	50.0	90.0
Cereal and cereal products, including						
Crackers and crispbread	0.0	0.0	5.0	25.0	15.8	30.0
Bread	56.2	80.0	0.0	0.0	0	0
Low carb bread	0.0	58.3	0.0	32.1	0.0	35.0
Cakes and sweet biscuits	17.0	52.8	0.0	10.0	0.0	0.0
Breakfast cereals	0.0	20.0	0	0	0	0
Pasta, rice, tortillas	0.0	0.0	0	0	0	0
Dairy products and substitutes	102.2	86.9	150.0	127.9	87.4	139.2
Cheese	26.8	20.0	28.0	48.0	37.0	33.3
Drinks, including						
Coffee, tea	182.6	65.5	192.0	73.0	194.5	74.4
Fruit and vegetable juice	0.0	0.0	0.0	0.0	0.0	0.0
Soft drinks and lemonade	0.0	192.0	0.0	0.0	0.0	0.0
Water	187.5	120.0	207.1	131.3	198.7	127.1
Alcoholic drinks (beer, wine, liquor)	0.0	100.0	0.0	0.0	0.0	0.0
Soup	31.3	250.0	0.0	250.0	141.3	250.0
Sugar, confectionary (sweet sauces)	6.8	15.0	0.0	2.0	0.0	7.0
Fats and oils, including	12.0	9.2	7.2	9.4	10.2	7.9
Butter	0.0	0.0	0.0	6.5	4.50	12.00
Margarine and cooking fats	0.0	3.5	0.0	1.0	0.0	0.0
Oil	0.0	0.0	0.0	1.0	0.0	2.0
Sauce	7.0	27.0	0.0	25.1	0.0	11.7
Fish, including	0.0	80.0	0.0	100.0	0.0	16.5
Oily fish	0.0	0.0	0	0	0	0
White fish	0.0	0.0	0.0	90.0	0.0	0.0
Meat and meat products	62.5	49.4	100.0	69.8	79.7	87.8
Soya and vegetarian products (including soya drinks)	0.0	0.0	0.0	0.0	0.0	0.0

4 Discussion

The results of these studies showed that the 6-month multidisciplinary group program designed to promote health literacy and lifestyle skills improves clinical parameters as well as quality of life in a substantial percentage of T2D patients after up to 24m. T2D is commonly considered a chronic progressive disease. Reduction of any medication dose is rare in regular clinical care. The present report signifies the potential of RD2N treatment as multicomponent lifestyle intervention to improve T2D in a significant number of patients, particularly in terms of medication use, metabolic control, as well as quality of life. Using a multidisciplinary approach, focussing on a broad spectrum of lifestyle skills rather than health literacy alone, as well as provision of biofeedback information on the effects of the intervention seems a viable approach.

We report real-life data, which is a strength of our study, as it reflects the impact of RD2N in daily clinical practice and thus provides evidence for real-life robust results. However, data collection in everyday life is less well-structured than in the context of a traditional clinical trial. The number of non-responders has been substantial in the present analyses, which probably biased the results since it is reasonable to suppose that less successful participants were more reluctant to respond to information requests.
Moreover, our analyses did not compare RD2N with another intervention, placebo and/or standard medical care. The lack of a control comparison hampers interpretation of the observations in terms of causality. However, application of the Bradford Hill criteria [23] to our study suggests a causal relationship between intervention and observed effects may be possible, as findings are biologically plausible and consistent over time. In addition, we cannot be sure that RD2N is any better than regular medical care in the Netherlands. However, reduction of GLmed in the course of time is rare in clinical practice, so the substantial decline in GLmed in response to RD2N treatment supports the idea that it contributes to better diabetes care.

5 Conclusion

With this Ekhagastiftelsen grant, we were able to show real-life robust, durable benefits of this lifestyle group program for T2D patients, particularly in terms of medication use, body weight and quality of life. This has contributed to building scientific practice-based evidence needed to incorporate this lifestyle intervention program as part of regular medical practice. As of 2020, the main health insurers fund this program and currently the Dutch Health Authority is investigating whether this program should be part of basic medical care.

6 Scientific publications created by this project

1. Pot GK, Battjes-Fries MCE, Patijn ON, Pijl H, Witkamp RF, de Visser M, van der Zijl N, de Vies M, Voshol PJ. Nutrition and Lifestyle intervention in type 2 diabetes: pilot study in the Netherlands showing improved glucose control and reduction in glucose lowering medication. *BMJ Nutrition Prevention & Health, 2019;2;43-50 (Open Access: doi: 10.1136/bmjnph-2018-000012)*
2. Pot GK, Battjes-Fries MCE, Patijn ON, van der Zijl N, Pijl H, Voshol PJ. Lifestyle medicine for type 2 diabetes: practice-based evidence for long-term efficacy of a multicomponent lifestyle intervention *BMJ Nutrition Prevention & Health, 2020;3(2):188-195 (Open Access: doi: 10.1136/bmjnph-2020-000081)*
3. Pot GK, Battjes-Fries MCE, Patijn ON, van der Zijl N, Pijl H, Voshol PJ. Leefstijlinterventie voor diabetes type 2: practice-based bewijs voor langere termijn effectiviteit van een leefstijlinterventie (Keer Diabetes2 Om). *[in Dutch] Huisarts en Wetenschap, 13 January 2021*
4. Pot GK, de Jong H, Battjes-Fries MCE, Patijn ON, Pijl H, Voshol PJ. Observational study on dietary changes of participants following a multicomponent lifestyle style intervention program (Reverse Diabetes2 Now). *Journal of Human Nutrition and Dietetics, 29 December 2021* https://doi.org/10.1111/jhn.12976

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