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Personalisation of the Dutch combined lifestyle intervention SLIMMER improves participant retention and weight loss in people at risk for cardiometabolic disease

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The Dutch combined lifestyle intervention (CLI) program SLIMMER is effective in changing lifestyle behaviour. However, achieving and maintaining a healthier lifestyle is difficult. Here, a personalised version of the SLIMMER CLI was evaluated for effects on lifestyle advice adherence as primary outcome and effects on weight loss, metabolism and inflammation as secondary outcomes. In this cluster-allocated controlled open-label parallel intervention study with 4 different health care sites per cluster, 61 participants in the personalised and 60 participants in the regular SLIMMER CLI (control) were included. Adults at risk for cardiometabolic disease were followed for 6 months. Adherence to lifestyle advice, Dutch Healthy Diet Index (DHDI), self-efficacy, lifestyle maintenance and quality of life (QoL) was assessed by questionnaires. Body composition and blood samples were measured at baseline and end of study. At 6 months the dropout rate was lower in the intervention group (11%) than in the control group (23%, $p<0.001$). Self-reported adherence to lifestyle advice and DHDI improved in both groups at 3 and 6 months, whereas self-efficacy and lifestyle maintenance did not change as a result of the intervention. At 6 months self-reported adherence to physical activity guidelines and QoL was higher in favour of control. At 6 months, body weight (-4.5 kg, $p=0.006$), BMI (-1.5 kg/m^2, $p=0.009$) and body fat percentage (-3.5%, $p=0.002$) improved more in the intervention than control group (-2.0 kg; -0.7 kg/m^2, and −1.0% respectively). No consistent difference in cardiometabolic or inflammatory outcomes was found between groups. Personalisation of an already effective CLI increased participants retention, unexplained by differences in adherence to lifestyle advice. Increased retention and a higher degree of weight loss could potentially lead to favourable long-term health outcomes.

Keywords Precision medicine, Primary health care, Weight loss, Lifestyle, Obesity, Risk factors

Abbreviations

AAT alpha	1-antitrypsin
AF	Alkaline phosphatase
ALAT	Alanine transaminase
ANOVA	Analysis of variance
ASAT	Aspartate transaminase
BMI	Body mass index
BP	Blood pressure
CLI	Combined lifestyle intervention
CVD	Cardiovascular diseases

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DHDI	Dutch healthy diet index
eGFR	Estimated glomerular filtration rate
GGT	Gamma-glutamyl transferase
GP	General practitioner
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein
hsCRP	High-sensitive C-reactive protein
IFN-γ	Interferon γ
IL	Interleukin
IP-10	IFN-γ-induced protein 10
IR	Insulin resistance
LDL	Low density lipoprotein
MPO	Myeloperoxidase
PFT	PhenFlex test
QoL	Quality of life
REML	Restricted maximum likelihood
SAA	Serum amyloid A
SLIMMER	SLIM iMplementation Experience Region Noord- en Oost-Gelderland
T2D	Type 2 diabetes
TG	Triglycerides
TNF-α	Tumor necrosis factor α

Overweight and obesity are risk factors for development of insulin resistance and type 2 diabetes (T2D) and are associated with a number of metabolic and cardiovascular risk factors[1]. Evidence is mounting that lifestyle changes can prevent or delay progression of metabolic disease. Previous studies showed that weight loss, changes in dietary intake, and increased physical activity resulted in long-term reduction in the incidence of T2D in persons with impaired glucose tolerance[2,3] and a reduction of low-grade inflammation[4].

Based on these results, combined lifestyle intervention (CLI) programs have been implemented within primary care in the Netherlands and are reimbursed for people with increased cardiometabolic risk or living with obesity. SLIMMER is one of those CLI programs. In the two-year SLIMMER program, adults with overweight (BMI 25–30 kg/m^2) in combination with cardiometabolic risk factors and/or comorbidities, or living with obesity (BMI ≥ 30 kg/m^2) are supported to improve their lifestyle with respect to dietary intake, physical activity, sleep, stress and social habits. The SLIMMER program resulted in on average 2.7 kg and 2.5 kg weight loss after 12 and 18 months, respectively[5].

Despite promising results of CLI programs, adherence is difficult, as represented by a dropout rate of 61% in Dutch CLI programs[6], with 26% of participants not completing the full program in the first year and another 35% of the participants not completing the second year[7]. The primary reason for dropout was lack of motivation[7]. Personalisation, i.e. adapting lifestyle advice to an individual's needs and preferences, may lead to better lifestyle advice adherence and contribute to achieving sustainable healthy lifestyle habits[8]. For acceptance of lifestyle advice, using behavioural change techniques is important for effective communication of the personalised advice[9]. Key behavioural determinants to establish behavioural maintenance include intrinsic motivation, self-efficacy, and creating a supportive environment[10]. Effective behaviour change techniques that could impact these determinants include goal setting, self-monitoring, self-evaluation, and provision of feedback and advice based on personal goals or specific behaviours[8,9]. Multiple systematic reviews indicated that personalised nutritional behaviour-change interventions based on information of a person's diet, biology and lifestyle improved both nutritional intake as well as health outcomes as compared to generalized nutritional advice[11–14]. Furthermore, blended care, defined as a combination of face-to-face care and dynamically tailored eHealth support adapted to behavioural, psychosocial and contextual factors of a person, has been shown to be more effective for lifestyle changes than face-to-face care only[15].

In the current study, the effect of a personalised SLIMMER program (intervention group) was assessed and compared to the regular SLIMMER program (control group) in a real-life primary care setting. On top of the regular SLIMMER CLI, personalisation included (1) personalised lifestyle advice based on (pre)diabetes subtyping (2) an extensive 360 degrees diagnosis, (3) personalised goal setting and monitoring, and (4) blended-care based personalised behaviour change support between the regular SLIMMER coaching sessions.

For an extensive 360 degrees diagnosis, insight into contextual lifestyle factors is important. Here, the 360 degrees diagnosis was used as basis to personalise lifestyle advice and to set personal lifestyle goals in shared decision between participant and health care professional. Furthermore, personalised dietary and physical activity recommendations were made based on the participant's insulin resistance (IR) subtype that arise from variations in genetics, phenotype, lifestyle and environment[16,17]. Research in primary healthcare practice showed that people with different IR subtypes benefit from differential dietary and physical activity recommendations[18], which resulted in remission and reversal rates of 33–75% of type 2 diabetes depending on the severity and subtype of T2D[19,20]. In addition, individual self-monitoring, personalised goal setting, behavioural monitoring, feedback and problem-solving were incorporated to achieve behaviour change. The personalised, sustainable behaviour change was supported by a blended care format, including digital and physical coaching.

The primary objective for this study was to assess effects of a personalised SLIMMER program on adherence to lifestyle advice, evaluated by subjective and objective changes in lifestyle behaviour. The secondary objective was to assess effects of a personalised SLIMMER on health status, measured by well-being, anthropometrics, clinical metabolic parameters and biomarkers related to low-grade inflammation. It was hypothesized that the personalised SLIMMER program would result in better adherence to lifestyle advice and result in greater improvements in body-weight and cardiometabolic health outcomes as compared to the regular SLIMMER program Fig.1.

Results

Participant flow

A total of 172 people were assessed for eligibility from which 27 people were excluded from the intervention group and 9 from the control group, because they declined to participate or did not meet inclusion criteria (Fig. 2). A total of 66 and 70 participants were allocated to the intervention or control group, respectively. In both groups, some participants did not start, because they were not interested anymore or due to COVID-19. Eventually, 61 and 60 participants received the allocated treatment, in the intervention and control group, respectively. In both the control and intervention group, some participants discontinued the SLIMMER program, and therefore were assigned as dropouts for our study. In the intervention group, 7 participants discontinued the intervention (reasons: SLIMMER program did not meet expectations, COVID), whereas in the control group, 14 participants discontinued the SLIMMER program (reasons: time constraints, not interested anymore). This dropout rate was significantly lower in the intervention group (11%) than in the control group (23%, $p < 0.001$). A modified intention-to-treat analysis was performed in which data from all participants were included with more than 80% of baseline data, including data from drop-outs with initially > 80% of data available. In the intervention, data from all participants, including from drop-outs was included in the analysis, whereas in the control data from all drop-outs and data from an additional 8 persons did not meet the modified ITT criteria. This resulted in 61 and 38 participants for analysis in the intervention and control group, respectively (Fig. 2).

Baseline characteristics

Table 1 shows baseline characteristics of the intervention group ($n = 61$) and control group ($n = 38$). Average age of the participants was 49.6 ± 11.4 and 48.8 ± 12.6 years in the intervention and control group, respectively. For both the intervention (33.0 ± 4.8 kg/m^2) and control group (34.6 ± 5.3 kg/m^2), mean BMI indicates that most participants had obesity. Indeed when looking at the BMI categories obesity class 1 (BMI 30–35 kg/m2) and class 2 (BMI > 35 kg/m2) had the highest representation in both groups (39.3% and 27.9% in intervention; 28.9% and 31.6% in control for obesity class 1 and 2 respectively). At baseline, BMI did not differ significantly between both groups ($p = 0.144$). Body weight showed a significant difference ($p < 0.038$) between the intervention group (95.5 ± 15.0 kg) compared to the control group (103.0 ± 16.9 kg). Fasting glucose and insulin did not differ between groups at baseline. However, there was a significant difference in HbA1c between intervention (36.4 ± 10.5 mmol/mol) and control group (40.9 ± 12.4 mmol/l, $p < 0.001$).

Subjective and objective assessment of lifestyle advice adherence

Subjective adherence to lifestyle advice guidelines

At baseline there was no difference in subjective adherence to the physical activity guideline between the intervention and control group (mean 3.5 vs. 3.2, Fig. 3A). Participants in the intervention and control group improved significantly on self-reported adherence to the physical activity guideline at 3 and 6 months compared to baseline ($p < 0.001$ for both time points, mean 4.1 (3 months) and 3.8 (6 months) in intervention and mean 4.1 (3 months) and 4.0 (6 months) in control). However, the change in self-reported adherence to the physical activity guideline from baseline to 6 months was significantly greater in the control than in the intervention

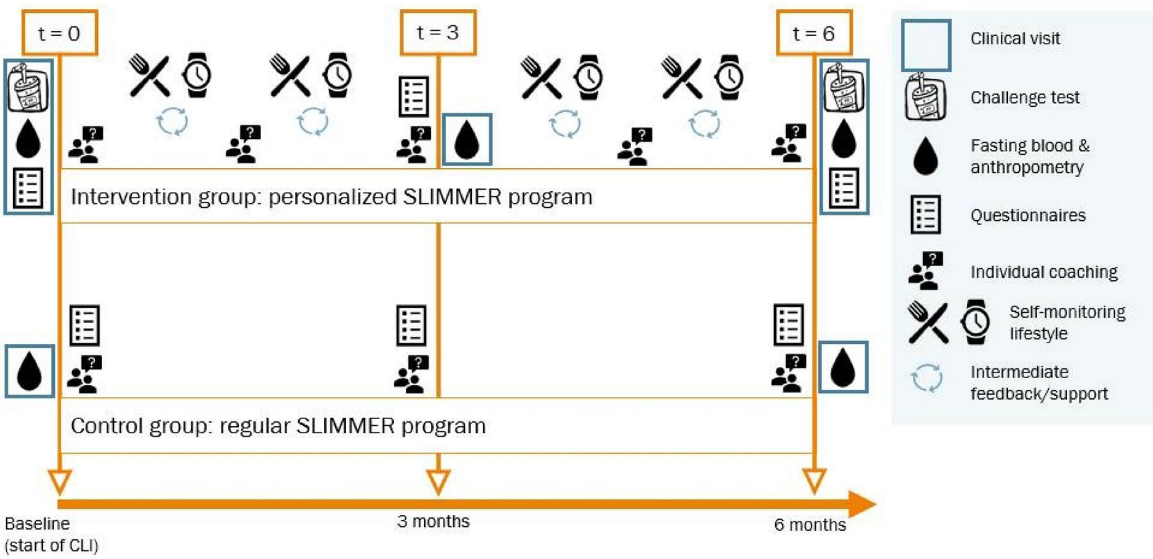

Fig. 1. Study design including an overview of study procedures of the intervention and control group. T = 0 is referred to as baseline, t = 6 is end of study.

	Intervention group ($n=61$)	Control group ($n=38$)
Female (%)	79	74
Age (years)	49.6 ± 11.4	48.8 ± 12.6
Body weight (kg)*	95.5 ± 15.0	103.0 ± 16.9
BMI (kg/m^2)	33.0 ± 4.8	34.6 ± 5.3
BMI category (n (%)) - Normal - Overweight - Obesity class 1 - Obesity class 2 - Obesity class 3	 2 (3.3%) 11 (18.0%) 24 (39.3%) 17 (27.9%) 7 (11.5%)	 0 (0%) 9 (23.7%) 11 (28.9%) 12 (31.6%) 6 (15.8%)
Waist circumference (cm)	109 ± 11	112 ± 12
Blood pressure (mmHg) - Systolic - Diastolic	 134 ± 16 84 ± 10	 138 ± 16 84 ± 10
Glucose (mmol/l)	5.96 ± 1.39	5.83 ± 1.97
Insulin (mIU/l)	13.5 ± 6.5	15.2 ± 7.2
HbA1c (mmol/mol)*	36.4 ± 10.5	40.9 ± 12.4
Total cholesterol (mmol/l)	5.20 ± 1.15	4.88 ± 1.08
eGFR (ml/min/1.73m^2)	93.9 ± 15.5	92.8 ± 15.6
Education level (n(%)) - High - Middle - Low	 29 (48%) 27 (44%) 5 (8%)	 14 (37%) 21 (55%) 3 (8%)

Table 1. Baseline characteristics of intervention and control group. Noted as mean ± SD, unless otherwise stated.* Indicates significant difference between intervention and control group at baseline ($p < 0.05$). HbA1c and glucose were used as covariates. BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin

group ($p < 0.05$). Also for the subjective adherence to the dietary guideline there was no difference at baseline between the intervention and control group (mean 3.7 vs. 3.9, Fig. 3A). Participants in the intervention and control group improved significantly on self-reported adherence to the dietary guideline at 3 and 6 months compared to baseline ($p < 0.001$ for both time points, mean 4.3 (3 months) and 4.2 (6 months) for intervention and mean 4.4 (3 months) and 4.3 (6 months) in control. There was no interaction effect between the two groups.

Objective adherence to dutch healthy diet index

At baseline, there was no difference in diet quality as assessed by the Dutch Healthy Diet Index (DHDI) between the intervention and control group (100.9 ± 17.8 vs. 94.0 ± 18.5), corresponding to an adherence of 60% to the Dutch Dietary Guidelines in both groups (Fig. 3B). There was a significant improved change at 3 months and 6 months in the intervention and control group and ($p < 0.05$ for both time points). There was no interaction effect nor statistical difference between intervention and control. At 6 months after the start of the intervention, scores were 107.3 ± 18.0 and 100.2 ± 15.0 for intervention and control groups, respectively. There were significant changes over time in following food groups: whole-grain products (significantly higher score at 6 months, but not different between intervention and control group), dairy products (significant changes over time, higher score change at 6 months in favour of control group), red meat (increase in score at 3 months, with significant higher score change for control vs. intervention group), and salt (increase in score at 3 months for both groups).

Self-efficacy

There was a significant difference in user-rated self-efficacy scores between intervention and control group, both on physical activity ($p = 0.02$; 4.8 ± 1.1 vs. 4.3 ± 1.2 (baseline); 4.8 ± 1.25 vs. 4.6 ± 1.3 (3 months); 4.6 ± 1.3 vs. 4.3 ± 1.2 (6 months) in intervention vs. control) and diet ($p = 0.02$; 5.0 ± 1.1 vs. 4.4 ± 1.3 (baseline); 4.8 ± 1.1 vs. 4.5 ± 1.5 (3 months); 4.7 ± 1.2 vs. 4.3 ± 1.2 (6 months) in intervention vs. control) (Fig. 4). Self-efficacy in the intervention group was higher at baseline and persisted higher over time as compared to the control group. No interaction effect was observed between the two groups over time, indicating that self-efficacy over time was not differentially affected by the intervention.

Maintenance of lifestyle behaviour change

Maintenance of lifestyle behaviour change remained similar between 3 and 6 months of the intervention (Fig. 5). Maintenance of physical activity advice at 3 months (mean 4.9 vs. 4.6 intervention vs. control) and at 6 months (mean 4.6 vs. 4.6 intervention vs. control), of dietary advice at 3 months (mean 4.8 vs. 4.5 intervention vs. control) and at 6 months (mean 4.4 vs. 4.2 intervention vs. control) and of personal goals at 3 months (mean 4.5 vs. 4.9 intervention vs. control) and at 6 months (mean 4.2 vs. 4.3 intervention vs. control) was not different between the groups, nor was an interaction or time effect observed.

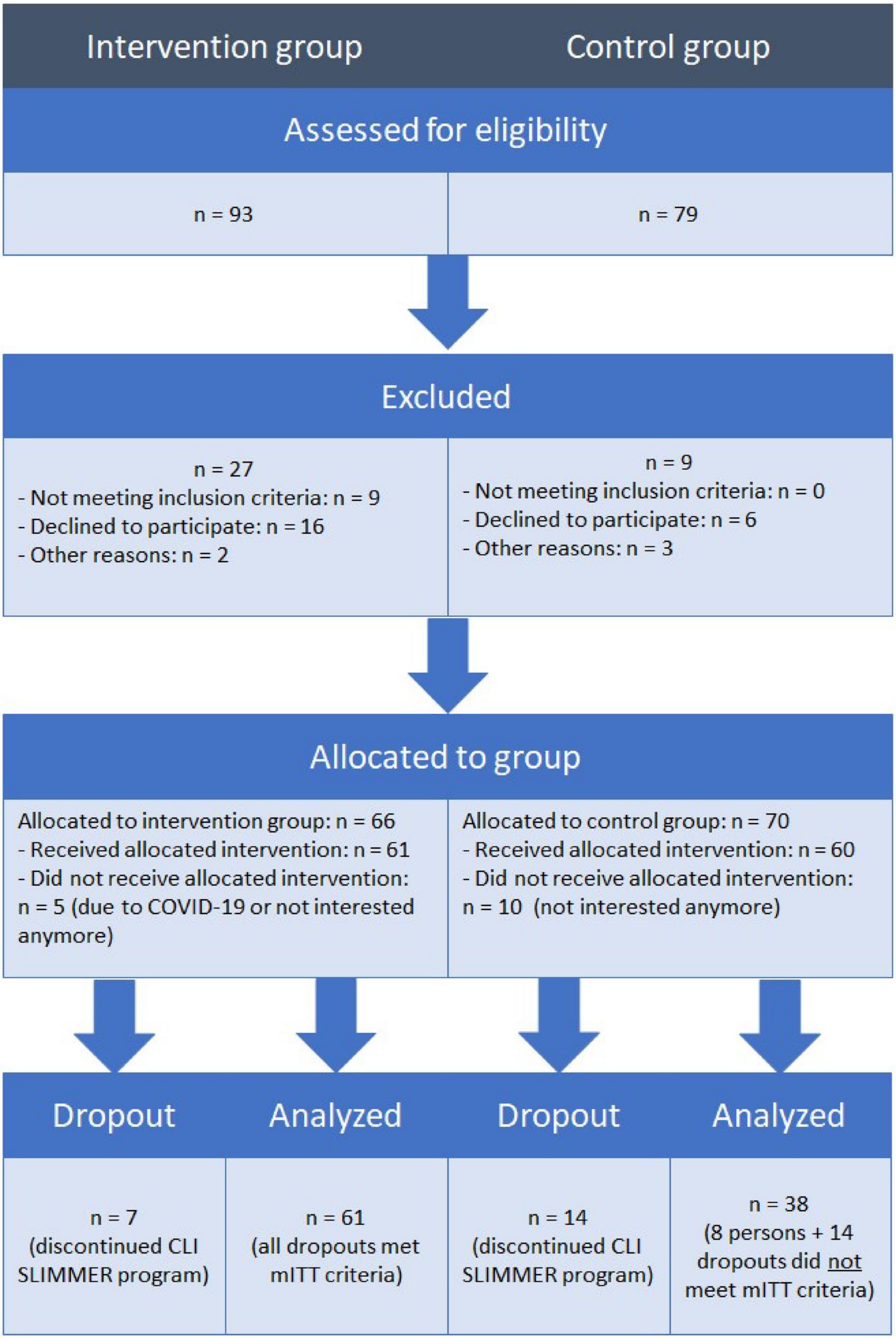

Fig. 2. Study flow diagram. Dropouts are defined as participants discontinuing the study or were lost to follow-up. Number of participants analysed is based on the modified intention-to-treat (mITT) principle in which participants are included in the analysis of whom > 80% of baseline data was available. CLI; combined lifestyle intervention.

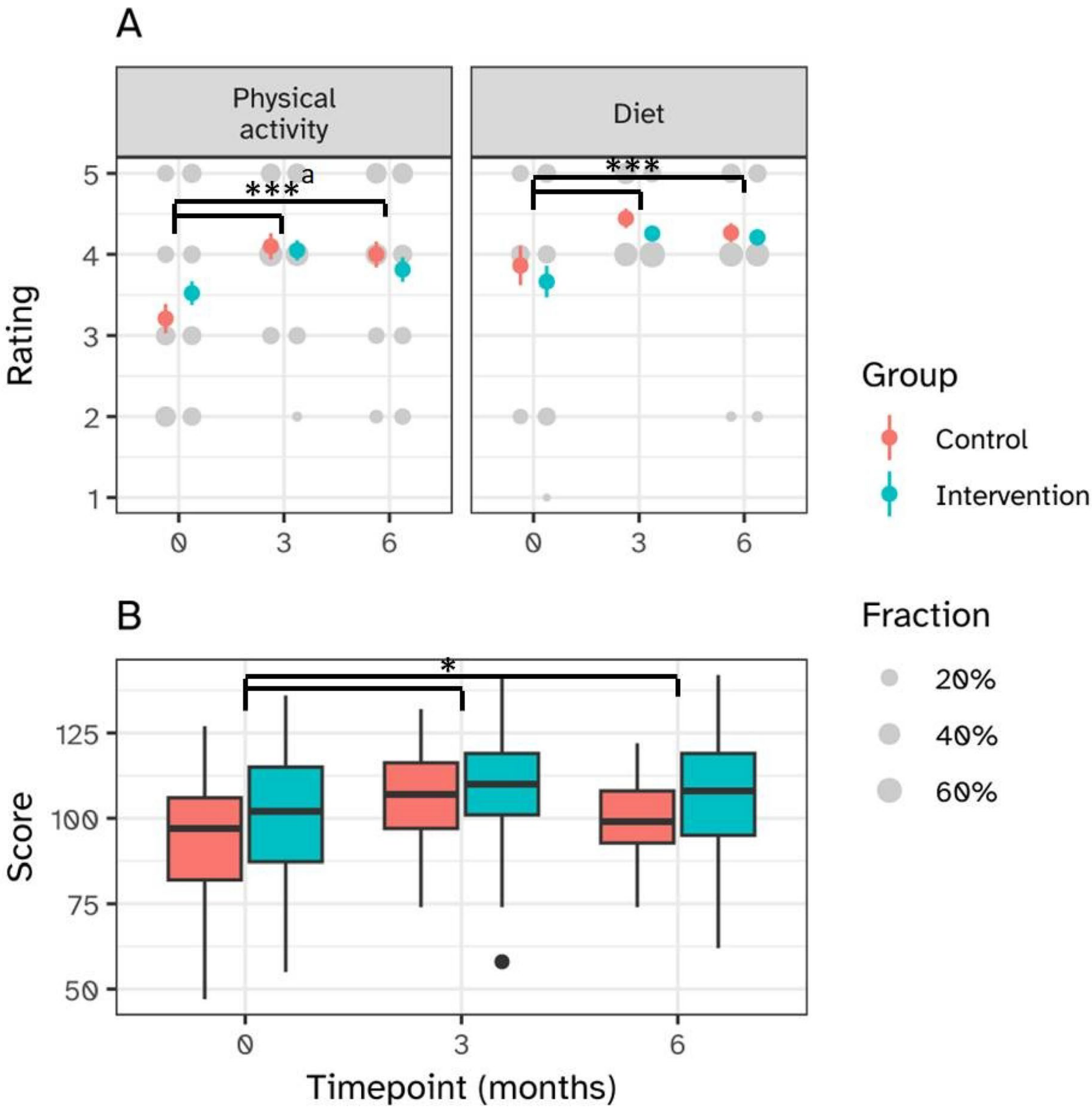

Fig. 3. Self-reported adherence to combined lifestyle program. Self-reported adherence to physical activity guidelines (A, left) and dietary guidelines (A, right) of intervention (blue) and control (red) participants over the course of the program on pre-defined scores from 1–5 with score 1 meaning "no and I have no intention" and score 5 meaning "yes regularly". Adherence to lifestyle advice was assessed at months 0, 3 and 6 by the questions " Do you practice physical activity regularly at the moment" and "do you currently have a healthy diet" from the subjective compliance and effort questionnaire. Grey circles represent the fraction size expressed as percentage. Total Dutch Healthy Diet Index (DHDI) score (B) for intervention (blue) and control (red) participants. X-axis: months after start intervention. Y-axis: mean DHDI score (0–160, higher score is better diet quality) ± SE. *p < = 0.05; **p < = 0.01; ***p < = 0.001; a: interaction effect p < = 0.05.

Quality of life

Quality of life (QoL) improved in both groups at 3 and 6 months compared to baseline (Fig. 6, $p<0.001$). At baseline, there was no difference between intervention and control group, with QoL mean score of 70 [40–99] in the intervention group and of 67 [21–99] in the control group. At 3 months QoL score improved on average with 7 points in intervention to a mean score of 77 [35–100] and with 12 points in control with a mean score of 79 [58–99]. At 6 months, the intervention group had a mean QoL score of 75 [26–93] and the control group had a mean QoL score of 79 [40–99]. The change from baseline to 6 months was significantly different between the two groups in favour of the control group ($p<0.05$).

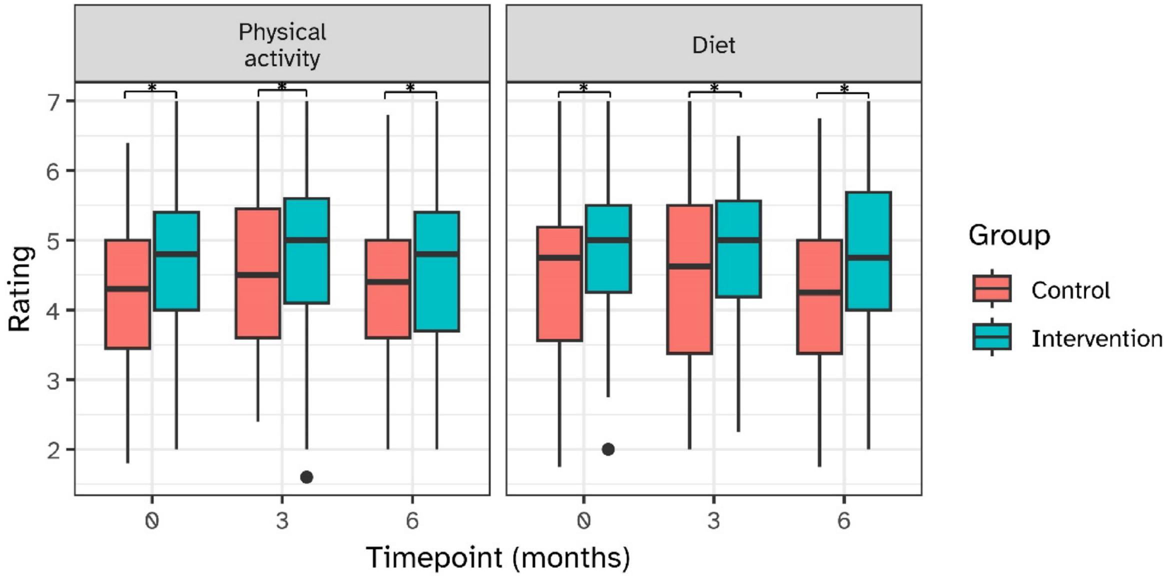

Fig. 4. Self-efficacy for combined lifestyle program. Self-efficacy for physical activity (left) and self-efficacy for diet (right) of intervention (blue) and control (red) over the course of the program. Self-efficacy for implementing lifestyle advice was assessed with the subjective compliance and effort questionnaire evaluated on months 0, 3 and 6 on a 7 points Likert scale. X-axis: months after start intervention. Y-axis: mean score on 7-points Likert scale ± SE.

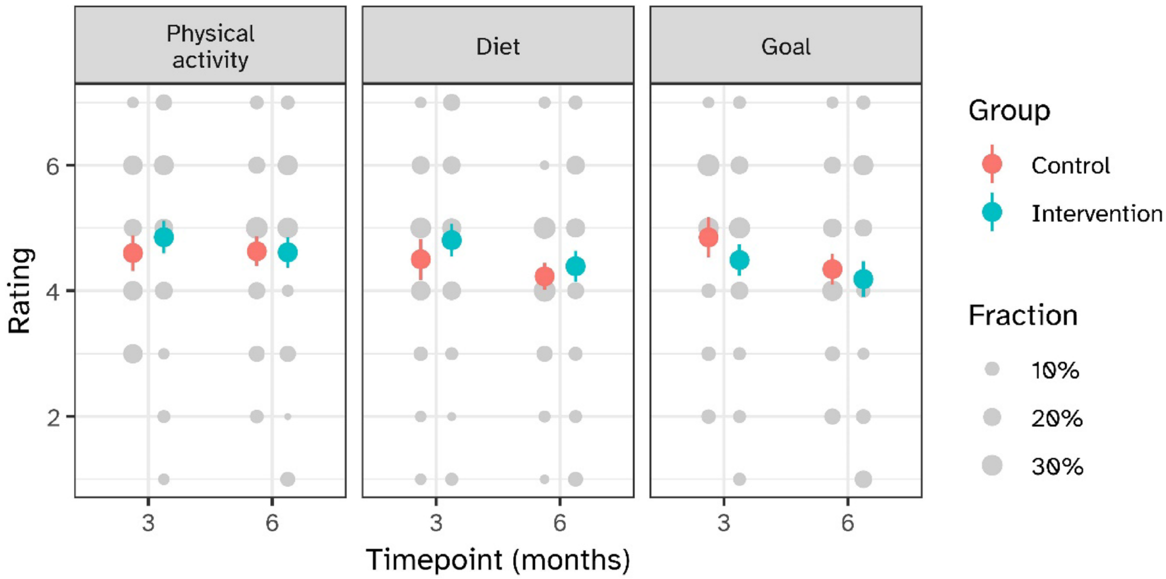

Fig. 5. Maintenance of lifestyle behaviour change. Maintenance of lifestyle behaviour change was determined by rating difficulty of maintaining the dietary and physical activity advice and the participant's own goals on months 0, 3 and 6 on a 7 points Likert scale. Level of difficulty of conforming to advice about physical activity (left); about diet (middle); maintaining participants own goal for a longer period of time (right) between intervention (blue) and control group (red). Grey circles represent the fraction size expressed as percentage, X-axis: months after start intervention. Y-as: mean score on 7-points Likert scale.

Appreciation of the lifestyle program

Overall, at six months, appreciation of intervention and control programs were rated 6.9 ± 1.6 and 7.0 ± 1.1 (scale 1–10), respectively. There was no significant difference in appreciation items between the intervention and control group (Table 2).

	Intervention group ($n=61$)	Control group ($n=38$)	p-value
Total score 1–10	6.9 ± 1.6	7.0 ± 1.1	0.884
Enjoyable 1–7	5.1 ± 1.3	5.3 ± 1.2	0.373
Difficult to understand 1–7	5.5 ± 1.4	5.8 ± 1.3	0.275
Difficult to execute 1–7	4.5 ± 1.6	4.5 ± 1.3	0.78
Interesting 1–7	5.0 ± 1.3	4.7 ± 1.4	0.458
Quality 1–7	4.5 ± 1.3	4.8 ± 1.3	0.32
Recommend 1–7	4.7 ± 1.8	4.9 ± 1.5	0.544
Follow again 1–7	4.6 ± 1.9	4.2 ± 1.7	0.294
Useful advice 1–7	4.8 ± 1.5	4.9 ± 1.1	0.612
Relevant advice 1–7	4.5 ± 1.6	4.5 ± 1.4	0.852
Free choice diet 1–7	5.9 ± 1.2	5.6 ± 1.2	0.272
Free choice exercise 1–7	5.9 ± 1.2	5.7 ± 1.2	0.363
Entertaining 1–7	5.9 ± 1.2	5.5 ± 1.4	0.127

Table 2. Appreciation scores of intervention and control group. Means ± SD.

	Intervention group		Control group		Interaction effect	
	Baseline	6 months	Baseline	6 months	Ratio ± SE	p-value
Body weight (kg)	95.5 ± 15.5	90.8 ± 13.5*	103.0 ± 16.9	101.0 ± 14.8*	0.97 ± 0.01	**0.006**
BMI (kg/m^2)	33.0 ± 4.8	31.5 ± 4.29*	34.6 ± 5.3	33.9 ± 4.6*	0.98 ± 0.01	**0.009**
Body fat (%)	42.7 ± 8.7	39.2 ± 7.6*	41.5 ± 8.4	40.5 ± 7.7	0.94 ± 0.02	**0.002**
Waist-hip ratio	0.92 ± 0.08	0.94 ± 0.08*	0.94 ± 0.08	0.92 ± 0.07	1.03 ± 0.01	**0.013**
Diastolic BP (mmHg)	84 ± 10	82 ± 10	84 ± 10	78 ± 9*	1.05 ± 0.02	**0.011**
Systolic BP (mmHg)	134 ± 16	128 ± 15*	138 ± 16	130 ± 14*	1.02 ± 0.02	0.323
Glucose (mmol/l)†	6.04 ± 1.51	5.75 ± 1.07*	5.94 ± 2.06	6.05 ± 2.55	0.97 ± 0.02	0.210
Insulin (mIU/l)	13.5 ± 6.5	13.5 ± 6.3	15.2 ± 7.2	12.5 ± 5.6*	1.22 ± 0.09	**0.012**
HbA1c (mmol/mol)†	36.4 ± 10.5	36.4 ± 5.8*	40.9 ± 12.4	41.9 ± 14.6	1.04 ± 0.02	**0.009**
Total cholesterol (mmol/l)	5.2 ± 1.2	5.14 ± 1.1	4.88 ± 1.08	4.85 ± 1.03	1.00 ± 0.03	0.877
HDL cholesterol (mmol/l)	1.35 ± 0.29	1.38 ± 0.29	1.22 ± 0.26	1.25 ± 0.25	1.00 ± 0.03	0.941
LDL cholesterol (mmol/l)	3.01 ± 0.94	3.02 ± 0.90	2.92 ± 0.91	2.90 ± 0.86	1.01 ± 0.04	0.740
Total cholesterol/HDL cholesterol ratio	3.84 ± 0.89	3.71 ± 0.83*	3.99 ± 0.94	3.86 ± 0.85	1.00 ± 0.03	0.915
Triglycerides (mmol/l)	1.44 ± 0.63	1.33 ± 0.56*	1.38 ± 0.62	1.31 ± 0.56	0.97 ± 0.05	0.584
eGFR (ml/min/1.73m^2)	93.9 ± 15.5	90.4 ± 14.3*	92.8 ± 15.6	91.2 ± 14.8	0.98 ± 0.02	0.310

Table 3. Comparison of clinical and metabolic measurements between intervention and control. Estimated marginal mean (EMM) ± SD, ratio ± SE is based on EMM. The ratio represents the relative change from baseline to 6 months in the intervention group compared to the control group, based on estimated marginal means. It is calculated on the log-transformed scale and back-transformed; values < 1.0 indicate a greater relative decrease (or smaller increase) in the intervention group. For example, a ratio of 0.90 indicates a 10% smaller change compared to control. P-value indicates interaction effect between the intervention and control group over the 6 months intervention period, significant p-values in bold. *Significant difference between baseline and 6 months within group. †Differed at baseline between intervention and control group and therefore used as covariate; covariate model used for body weight, BMI, body fat, triglycerides, eGFR. BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein

Metabolic outcomes

Beneficial changes in metabolic measurements over 6 months were observed in both the intervention and control group (Table 3). In both groups, body weight decreased significantly, from 95.5 ± 15.0 kg to 90.8 ± 13.5 kg in the intervention group ($p<0.001$) and from 103.0 ± 16.9 kg to 101.0 ± 14.8 kg in the control group ($p=0.007$). Body weight loss was significantly higher in the intervention group compared to the control group (4.7 kg, 4.9% body weight change vs. 2.0 kg, 1.9% body weight change; $p=0.006$). Body fat percentage and waist-hip ratio significantly changed in the intervention group only (−3.5%; $p<0.001$ and $p=0.025$, respectively) and these changes over time were significantly different from the control group ($p=0.002$ and $p=0.013$, respectively). In the intervention group, 81% of participants lost weight: 37% ($n=20$) lost 0–5%, 33% ($n=18$) lost 5–10%, and 11% ($n=6$) lost over 10% of body weight. In the control group, 77% of participants lost weight, with 57% (n=17) in the 0–5% category and 10% ($n=3$) in the 5–10% and 10% (n=3) in the > 10% body weight loss categories. In both groups systolic blood pressure decreased, but only the control group showed a significant reduction in diastolic blood pressure ($p < 0.001$), which differed significantly from the intervention group ($p = 0.011$).

Fasting glucose significantly decreased in the intervention group ($p = 0.003$), but this change over time was not significantly different from the control group ($p = 0.210$). Insulin significantly decreased in the control group ($p = 0.002$), but not in the intervention group ($p = 0.968$), yet all within normal ranges. This change was significantly different between the groups ($p = 0.012$). HbA1c showed a significant interaction effect between the two groups ($p = 0.009$), with maintained concentrations in the intervention group, whereas concentrations in the control group non-significantly increased.

No changes in total, HDL and LDL cholesterol were found. Cholesterol ratio, TG and eGFR showed significant decreases in the intervention group over time ($p = 0.038$, $p = 0.015$ and $p = 0.003$, respectively), which were not observed for the control group ($p = 0.133$, $p = 0.205$ and $p = 0.247$, respectively). However, these changes did not differ significantly from the control group ($p = 0.915$, $p = 0.584$ and $p = 0.310$, respectively).

Inflammation

Changes in inflammatory biomarkers were found in both groups (Table 4; Fig. 7). Leptin decreased significantly in the intervention group ($p < 0.001$), while leptin increased markedly, but not significant, in the control group. Adiponectin significantly increased in both groups ($p < 0.001$ for intervention group and $p = 0.012$ for control group). Resistin increased in both groups at 6 months, but to a differential extent ($p = 0.006$), with significantly increased concentrations in the control group and no significant increase in the intervention group. Furthermore, in the intervention group, but not in the control group, hsCRP ($p = 0.016$) and AAT ($p = 0.002$) significantly decreased from baseline to 6 months. E-selectin significantly decreased in both groups ($p < 0.001$ for intervention group, $p = 0.012$ for control group).

Discussion

The effects of personalisation of the proven effective CLI program SLIMMER was assessed on lifestyle advice adherence and cardiometabolic outcomes. The most important observation was the difference in dropouts between intervention and control group ($p < 0.001$), being 11% in the intervention group *versus* 23% in the control group. Main reasons for premature dropout included time constraints and dissatisfaction with the program or group. The dropout percentage of 11% in the intervention is not only lower than the control group, but also lower than average dropout rates (26%) as reported for CLIs in the first year[7]. This suggests that personalisation prevents premature dropout of the lifestyle program and increases retention. A clear difference between the intervention and control group was the amount of contact and attention the participants received, which may contribute to these results. Interestingly, personalisation of the CLI was not related to differences in adherence to lifestyle advice assessed by questionnaires on self-reported adherence, self-efficacy and maintenance to diet and physical activity advices. Subjective adherence to the combined lifestyle program as well as the objective DHDI score improved in both groups at 3 and 6 months, whereas subjective self-efficacy and maintenance to diet and physical activity advices did not change as a result of the intervention. For subjective adherence to physical activity guidelines a greater change at 6 months was observed in favour of the control group. These results were surprising as it has repeatedly been shown that behavioural treatment strategies, with emphasis on self-efficacy, motivation and feedback - as was implemented in the personalised SLIMMER - improve adherence to lifestyle

	Intervention group		Control group		Interaction effect	
	Baseline	6 months	Baseline	6 months	ratio ± SE	*p*-value
Leptin (ng/ml)	47.5 ± 24.5	37.5 ± 24.5*	45.0 ± 43.6	51.5 ± 43.7	0.90 ± 0.07	0.162
Adiponectin (μg/ml)	2.95 ± 1.40	3.40 ± 1.65*	2.70 ± 1.43	3.12 ± 1.73*	1.01 ± 0.05	0.810
Resistin (ng/ml)	16.8 ± 9.36	17.8 ± 8.9	14.0 ± 7.38	18.0 ± 7.51*	0.87 ± 0.04	**0.006**
hsCRP (μg/ml)	3.96 ± 4.00	3.18 ± 4.75*	2.54 ± 3.43	2.33 ± 3.50	0.89 ± 0.13	0.428
IL-6 (pg/ml)	0.99 ± 0.66	0.97 ± 0.68	0.77 ± 0.57†	0.70 ± 0.40	1.07 ± 0.10	0.443
TNF-α (pg/ml)	1.51 ± 0.33	1.49 ± 0.58	1.59 ± 0.41	1.60 ± 0.38	1.01 ± 0.04	0.900
IFN-γ (pg/ml)	4.40 ± 3.44	4.41 ± 5.24	4.12 ± 2.17	3.87 ± 2.71	1.02 ± 0.13	0.870
IP-10 (ng/ml)	1.76 ± 0.74	1.93 ± 0.89	1.73 ± 0.59	1.71 ± 0.75	1.06 ± 0.07	0.402
MPO (ng/ml)	29.2 ± 11.0	29.8 ± 14.7	31.6 ± 12.8	29.7 ± 10.4	1.01 ± 0.07	0.902
E-selectin (ng/ml)	11.10 ± 6.94	9.34 ± 4.76*	11.70 ± 5.73	10.60 ± 6.99*	0.95 ± 0.04	0.158
AAT (mg/ml)	2.57 ± 0.77	2.26 ± 0.78*	2.42 ± 0.92	2.24 ± 0.99	0.95 ± 0.05	0.331
Haptoglobin (μg/ml)	1100 ± 676	1210 ± 541	972 ± 360	1020 ± 577	1.00 ± 0.08	0.958
SAA (μg/ml)	5.29 ± 5.96	5.41 ± 6.73	6.40 ± 6.11	4.97 ± 6.25	0.98 ± 0.11	0.873

Table 4. Comparison of inflammatory biomarkers between intervention and control group. Median with IQR at baseline and 6 months of inflammation markers. P-value indicates interaction effect between the intervention and control group over the 6 months intervention period, significant p-values in bold. * Indicates significant difference between baseline and 6 months within group. Covariate model used for E-selectin. † Indicates significant differences at baseline between intervention and control group. AAT, alpha-1-antitrypsin; hsCRP, high-sensitive C-reactive protein; IFN-γ, interferon γ; IL-6, interleukin 6; IP-10, IFN-γ-induced protein 10; MPO, myeloperoxidase; SAA, serum amyloid A1; TNF-α, tumor necrosis factor α

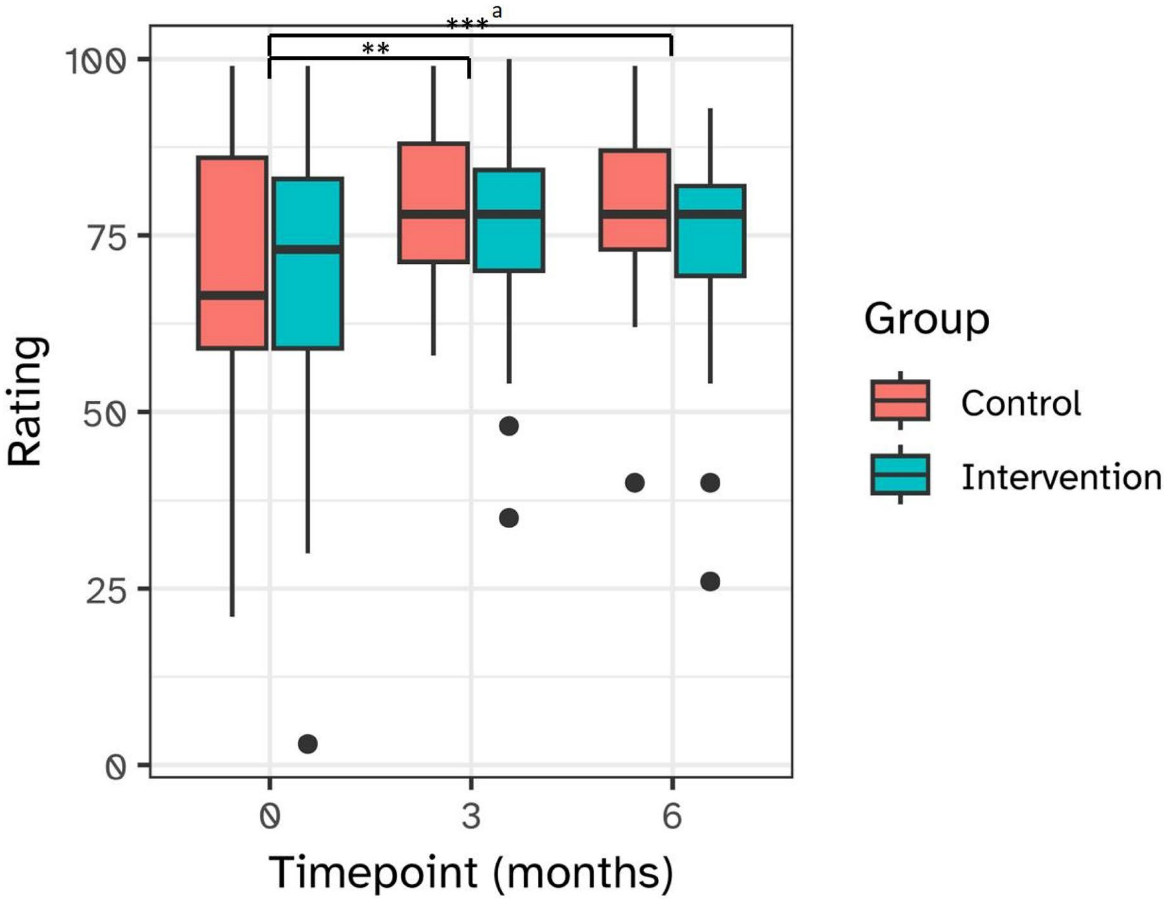

Fig. 6. Quality of life during study. Quality of life scored using the EQ-5D questionnaire for the intervention (blue) and control group (red). X-axis: months after start of intervention. Y-axis: box plots based on first quartile (q25) and third quartile (q75) with median quality of life score (scale 0–100) and minimum and maximum values represented. Dots indicate outliers (q25-1.5*(q75-q25) or q75 + 1.5*(q75-q25)). Blue box plots represent intervention and red box plots represent control. *p < = 0.05; **p < = 0.01; ***p < = 0.001; a: interaction effect p < = 0.05.

advice[9,21]. QoL improved in both groups with approximately 8 points (11%), but this was mainly maintained at 6 months in the control group. A change in QoL of 8 points is in accordance to the average score for QoL of Dutch CLIs[7] and clinically relevant. A combination of subjective and objective evaluation of adherence may be sensitive to biases such as recall or social desirability. There would, however, be no reason why possible biases would differ between intervention and control group. This type of self-assessment have been shown to be meaningful and a valid way to assess self-management behaviour[22].

Another important observation is that the personalised SLIMMER program improved body weight, BMI and body fat percentage to a larger extent than the regular SLIMMER program. Body weight decreased with 4.7 kg (4.9%) in the intervention group versus 2 kg (1.9%) in the control group. Body weight loss in the intervention group is higher than average body weight loss after 6 months of any CLI in the Netherlands (3.4%), suggesting positive effect of personalisation. As overweight is associated with development of cardiometabolic diseases, this is an important and clinically relevant outcome.

Several biomarkers related to cardiometabolic health showed improved values in both groups after 6 months of the program, but did not show differences between both groups, except the differences in weight loss. A possible explanation for absence of clear improvements in cardiometabolic outcome parameters in the intervention group as compared to control group despite weight loss differences can be related to metabolic heterogeneity within the groups. Presumably both groups included persons with a healthy metabolism as well as persons with disturbed metabolism. A person who is metabolically healthy at baseline may show fewer improvements in contrast to a person that has a higher risk for developing comorbidities[23]. This difference may be further exaggerated by the higher dropout rate in the control group. Possibly, people who did not experience improvements were less motivated to continue with the program, leaving a relatively high degree of participants with beneficial changes in the control group. The lower standard deviation (i.e. lower variation) within the control participants may reflect this. Importantly, it should be taken into account that the intervention group is compared to a control group that followed an already proven effective program.

The SLIMMER program, and in particular the personalised SLIMMER program, led to minor, but favourable alterations in low-grade inflammatory markers. The acute-phase protein SAA is a clinically useful marker of inflammation[24]. Plasma concentrations of SAA in healthy participants are usually very low, but increase in response to inflammation[24]. In the present study, SAA concentrations at baseline are above the threshold for healthy people and remained elevated over the course of the intervention in both groups, which indicates ongoing (low-grade) inflammation. In the intervention group, serpin A1/AAT[25], leptin[26], E-selectin[27], hsCRP[25] and adiponectin[28] levels improved, whereas in the control group E-selectin and adiponectin improved and resistin[29] deteriorated. This suggests that specially the personalised SLIMMER program resulted in a slightly improved inflammatory state. This may be explained by the difference in body weight loss. However, multiple inflammatory markers including TNF-α, haptoglobin, MPO, IP-10, SAA and IFN-γ did not change during the 6 months intervention in either group. Therefore, the inflammatory results should be carefully interpreted and need further follow-up, e.g. in a longer study period or using more inflammatory parameters.

The strength of this study is that it was a real-life study that took place in a primary care setting and included all study participants that were referred by their GP to follow the SLIMMER program. Although randomised controlled trials (RCTs) are the accepted golden standard for research, the external validity for assessing effectiveness of lifestyle interventions is often limited, as they typically involve individuals who are already motivated to change their behaviour, are less severely ill, and participate under idealized conditions. This study therefore reflects the actual population enrolled in this CLI program under real-world conditions, enhancing its generalizability and offering valuable insights into how the program can be optimized for routine clinical practice. There was a close collaboration with the healthcare professionals from the different SLIMMER practices, who were trained by researchers in motivational interviewing, using the 360 degrees diagnosis and providing motivational exercises. Using this method, interindividual differences between treatment of participants was kept to a minimum. Although the relatively modest sample size limits broad generalizability, the repeated-measures design and number of participants provided adequate internal validity by precise estimation of within-person changes over time. The study was deliberately designed as a pragmatic real-world evaluation, and sample size and implementation choices were made to ensure feasibility within routine primary care settings. However, conducting a pragmatic real-world evaluation also introduced several study limitations. A major weakness is the absence of random assignment, which may have led to systematic differences between healthcare sites offering the personalized CLI and those in the control group, thereby introducing potential bias. It is worth mentioning that this study was conducted across multiple practices, which generally operate under the same protocol. Additionally, the inclusion and exclusion criteria were broader for the personalised group, which could have further contributed to selection bias. Another limitation is the inability to disentangle what part of personalisation contributed to the observed results, e.g., whether it was the enhanced diagnosis at baseline or the personalised behaviour support that contributed most to the difference in program retention and weight loss outcomes. Furthermore, incomplete information was collected by the health care professionals on compliance to the SLIMMER program, e.g. how well participants participated in the different appointments. Combined with the large number of dropouts or persons that did not meet modified ITT criteria in the control hindered per protocol evaluation of the data. Sample size calculations indicated that 44 participants per group were needed to detect a significant effect in lifestyle adherence, the primary outcome. However, due to high dropout rates and missing baseline data, the control group included only 38 participants, potentially limiting the ability to observe the expected effect which weakened the study's internal validity. Lastly, as it was not feasible to use the SQUASH algorithm to compare the amount of objective physical activity between intervention and control group, these results were not presented and not taken into account in the conclusion. Activity tracker data (not shown) within the intervention group showed increased physically active behaviour especially in the month before start of the SLIMMER intervention, which was not maintained in the six months of the intervention itself[36]. This data, however, was not available for control. It is a limitation that we did not have reliable information on objective amount of physical activity. The measure of adherence – defined as a composite of subjective perceptions and objective measures of compliance with dietary and physical activity guidelines - relied heavily, particularly for physical activity, on a non-validated self-reported item, which may have limited the reliability of the assessment. The current study was performed during the COVID pandemic, which may have influenced study outcomes and hamper interpretation of the results. To evaluate this effect, a questionnaire was filled out by the intervention participants at their 6-months visit. Most participants indicated that COVID did not influence their changes in diet or exercise. Some participants reported a negative influence of the COVID pandemic on participating in the SLIMMER program, due to closing of sport facilities or increased stress. The control group participated in the same study period, and it is therefore assumed they were similarly affected by COVID-regulations. So, it can be concluded that found effects can be extrapolated to a period without COVID-regulations.

In conclusion, a major finding in this controlled intervention study was the remarkable lower dropout rate in the intervention group, suggesting that the personalized approach resulted in increased program retention. The personalized intervention included increased individual attention, blended behavior change support and self-monitoring which may have contributed to the improved retention. The higher extent in program retention was, however, not explained by improved subjective and objective primary outcome measurements related to self-reported adherence, self-efficacy and maintenance for lifestyle advice. In contrast, self-rated adherence to physical activity guidelines and Quality of Life improved to a higher extent in control at 6 months. In addition, the personalized SLIMMER program improved secondary outcome measurements related to body weight, BMI and body fat percentage, more than in the regular SLIMMER program. Albeit differences in weight loss this did not translate into additional beneficial changes in cardiometabolic outcomes for the personalized SLIMMER within this six months' time period. Taken into account that the personalized intervention group was compared to a control group that followed an already proven effective lifestyle program, observed effects may stress the

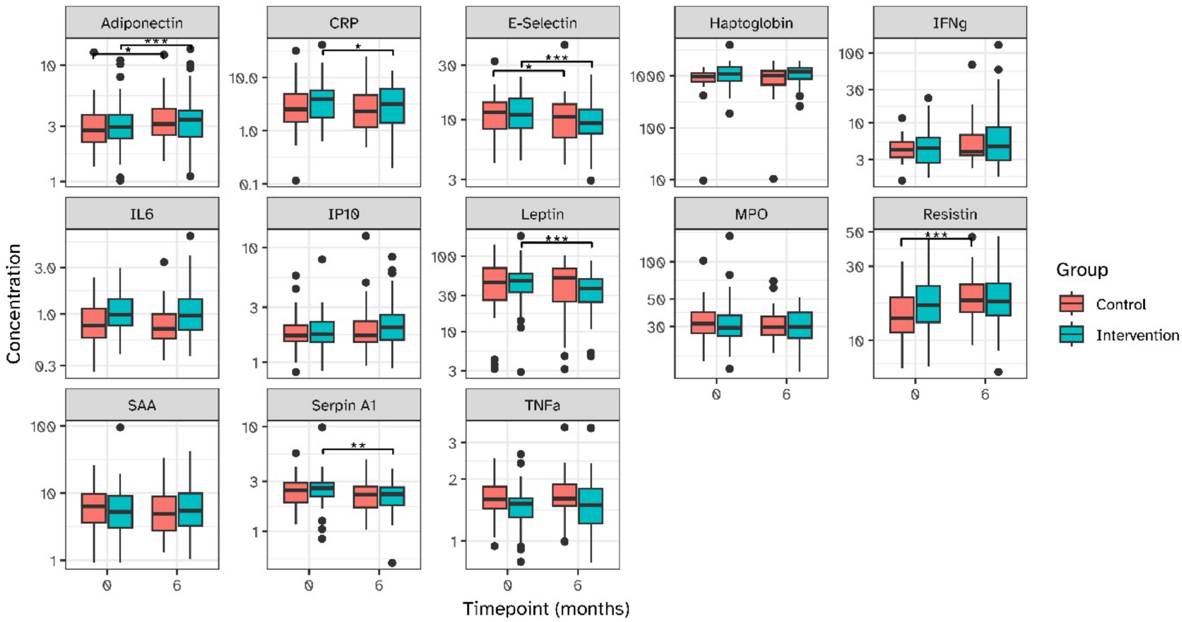

Fig. 7. Plasma inflammatory biomarkers. comparison of inflammatory biomarkers between intervention (blue) and control group (red) over 6 months intervention. CRP; C-reactive Protein, IFNg; Interferon- γ, Il; Interleukin, IP10; IFN-γ-induced protein 10, MPO; myeloperoxidase, SAA; serum amyloid A1, TNFa; tumor necrosis factor α, *p < = 0.05; **p < = 0.01; ***p < = 0.001.

importance of personalization of a CLI since the effects related to weight loss and body composition are clinically relevant.

Methods

Recruitment, study population and treatment allocation

In November 2020 the study was approved by the Dutch Medical Ethics Committee (METC Brabant, NL75482.028.20) and registered at International Clinical Trials Registry Platform with ID NL-OMON51873 (7/12/2020).

Participants in this study were patients that were referred by their general practitioner (GP) to participate in the SLIMMER program. Inclusion criteria for the SLIMMER program were male and female aged 18–70 years with a BMI > 25 kg/m^2 in combination with an increased waist circumference (female > 80 cm, male > 90 cm), or BMI > 25 kg/m^2 plus one or more diseases that are associated with overweight, or people living with obesity (BMI > 30 kg/m^2). Exclusion criteria for the SLIMMER program were psychosocial problems interfering with complying to the program. For the intervention group additional inclusion criteria were able to use online technology on a tablet or a PC/laptop which has good access to the internet; in possession of a smartphone; willing to comply to study procedures and proficient in the Dutch language (speaking and reading). For the intervention group, additional exclusion criteria included a planned surgery during the study period, regular use of anti-inflammatory drugs, corticosteroids, TNF-α blockers and salicylates and having a chronic inflammatory disease or bowel disease. Written informed consent was obtained from all participants. Participants were recruited from the area of Utrecht and Zutphen, the Netherlands, between March 2021 and November 2022. Participants were allocated to intervention or control group based on their primary care centre. Health care professionals providing the SLIMMER CLI were contacted and involved in the study. The health care professionals interested in the study and willing to be involved as an intervention site, were provided with a training to enable them to provide participants with the personalized advice of the SLIMMER program. Per study group four different healthcare sites recruited participants who would start the SLIMMER CLI at their location, for the study. The study period took place during the COVID-19 pandemic, where the Dutch government took different measures such as lock downs and restrictions for sport facilities or group based activities, thereby also affecting the SLIMMER program.

Trial design and intervention groups

This was an open label cluster allocated controlled parallel study with an intervention and a control arm (Fig. 1). In the current study, participants were followed during the first six months of the two-year SLIMMER program[30], which consisted of weekly group sessions about nutrition and physical activity, and three to five individual appointments with a dietician (sometimes adapted due to COVID-19 measures). All participants had already been referred to the SLIMMER program by their GP. Participants started the program at different time points between March 2021 and November 2022. All participants filled in multiple online questionnaires at baseline, at t = 3 and t = 6 months. These included the EQ-5D a 5-dimension health-related quality of life instrument[31], the Eetscore to assess diet quality based on the Dutch Healthy Diet Index (DHDI)[32], a questionnaire on subjective compliance and effort and an appreciation questionnaire (see Supplementary Materials for full details). Participants in the control group followed the regular SLIMMER program, where for study purposes blood was drawn in overnight fasted state at a local clinical lab (Saltro) and anthropometrics and blood pressure (Medisana MTX) were measured by the involved healthcare professionals at baseline (t = 0) and at six months. The intervention group followed the SLIMMER program to which validated personalisation tools were added (see personalised SLIMMER intervention). Participants from the intervention group came to the research facility one month before the start of the SLIMMER program after an overnight fast. The day before the visit, participants from the intervention group had to consume a low fat evening meal and had to refrain from alcohol and exercise. At the start of test days, wellbeing, adverse events and follow-up of study rules was systematically checked. Subsequently, anthropometrics were measured, followed by the PhenFlex test (PFT). Participants from the intervention group could self-monitor body weight, physical activity and food intake during the entire study. At t = 3 months, participants from the intervention group were asked to have blood drawn in a fasted state at a local clinical lab (Saltro). At t = 6 months, the test day at the research facility was repeated.

Personalised SLIMMER intervention

The following validated personalization tools were used for the personalised SLIMMER intervention: (1) Subtyping based on a PFT; a mixed-meal challenge test (PFT, FoodPilot, Melle, Belgium), validated against an oral glucose tolerance test, was included to determine the IR subtype[17]. First, a venous canula was placed, from which fasted blood samples were taken. Next, participants consumed the PFT, after which blood was drawn at 30, 60, 120, and 240 min after start of consumption[17]. Based on plasma glucose and insulin measurements, it was calculated whether participants had (pre)diabetes, and if so, which organs were affected[19]. Based on the IR subtype, a personalised dietary and/or physical activity advice was given at the start of the SLIMMER program[19]. For individuals without IR dietary strategies focused on weight reduction. Participants could choose from all available dietary options (Mediterranean diet, a low-calorie diet, a carbohydrate-restricted diet, or intermittent fasting), as all of these are supported by evidence showing their effectivenss in weight and metabolic risk reduction[33–35]. This dietary advice was further tailored to personal preferences and context by the dietician. In participants with liver IR and normal beta-cell function, rapid weight loss was prioritized[36], and a low-calorie diet was recommended as the most effective approach, with intermittent fasting offered as an alternative when more suitable to individual preferences[34]. For those with muscle IR and normal beta-cell function, the Mediterranean diet was emphasized[37,38], and rapid weight loss was not a primary goal. In cases of impaired beta-cell function, a carbohydrate-restricted diet was recommended to improve glycemic control and reduce fasting glucose levels[39]. Participants with combined phenotypes could choose from the options available to their respective isolated IR or isolated beta-cell function groups. Physical activity recommendations were also phenotype-specific. Participants with no IR were encouraged to meet general physical activity guidelines[35]. For those with liver IR, with or without muscle IR, a combination of endurance and resistance training was recommended to improve insulin sensitivity[40,41]. In cases of muscle IR, endurance training was prioritized, supplemented by resistance training once per week[42]. For individuals with impaired beta-cell function, with or without organ-specific IR, a higher volume of physical activity was recommended. This included longer-duration endurance training, based on evidence suggesting a dose-response relationship between activity volume and insulin sensitivity improvements in advanced T2D[40,41]. The intensity of exercise was considered less critical than the total volume. (2) 360 degrees diagnosis; the 360 degree diagnosis tool is described extensively elsewhere[43]. In short, the 360 degrees diagnosis is a web-based tool for shared-decision making between patient and health care professional based on a holistic diagnosis covering the 4 domains body, thinking and feeling, behaviour and environment. The domain body focuses on physiological health and includes biomedical data such as HbA1c, blood lipids and blood pressure. Outcomes of the domains focusing on psychological health, lifestyle behaviour and socio-economic factors were the output of validated online questionnaires filled in by the participant. The 360 degree diagnosis tool is composed of a total of 20 factors divided over the 4 domains. For each domain factor evidence-based cut-offs were developed based on decision rules allowing for categorization as unhealthy (red), healthy (green) or in-between (orange). The 360 degree diagnosis was included at t = 0 and t = 6 for shared decision making between participants and healthcare professionals, to set personal lifestyle goals (t = 0) and to evaluate outcomes related to physiological health, thinking and feeling, lifestyle behaviour and environment. (3) Self-monitoring; participants were equipped with a Fitbit Charge 4 activity tracker (Fitbit Charge 4; Fitbit Inc., San Fransisco, CA, USA) and a smart-scale (Fitbit Aria Air; Fitbit Inc., San Francisco, CA, USA), and were stimulated to use a food-diary app for food-logging (FatSecret made available via the HowAmI-application, TNO, Leiden, the Netherlands). In this way, participants could monitor their physical activity (step count), food intake and body weight for their own motivation. (4) Personalised behavioural support (blended care format); participants had access to personalised behavioural change support via the HowAmI-app (TNO, Leiden, The Netherlands), where participants could set personal lifestyle goals. Participants received notifications for data-entering. Goal achievement could be tracked daily, which included feedback and reinforcement. Data from the activity tracker, food-logging app and smart scale was automatically synchronized to a personal internet portal. This portal was used during coaching sessions to evaluate personal lifestyle goals and to assess possible barriers in goal adherence and to adapt goals if desired. Furthermore, it served as input for dynamic tailoring during coaching sessions between participant and healthcare professional which took place at t = 6 weeks, t = 12 weeks, t = 18 weeks and t = 24 weeks. Healthcare professionals were trained in interpreting the results from the 360 degrees diagnosis and in motivational interviewing, and were supported with behavioural change exercises to support participants with enhancing motivation, self-efficacy, planning, problem solving, relieving stress, arranging social support, or improving mood.

Measurement of study outcomes

Adherence to lifestyle advice

The primary outcome of the current study was adherence to lifestyle advice. This was operationalized by combining subjective perceptions of adherence with validated and objective measures of dietary and physical activity adherence. Subjective adherence to the dietary and physical activity guidelines was assessed at months 0, 3 and 6 by questions "Do you practice physical activity regularly at the moment [*Regular physical activity is defined as moderate exercise for 30 minutes on at least 5 days, but preferably 7 days a week*]" and "do you currently have a healthy diet [*A healthy diet is defined as eating according to Dutch Healthy Eating guidelines and using limited concentrations of salt (source: Nutrition Center)*]" from the subjective compliance and effort questionnaire (pre-defined scores from 1 to 5; see Supplementary Materials). Given that all dietary recommendations in our study were grounded in the Dutch Dietary Guidelines, objective adherence to these guidelines was assessed using the Dutch Healthy Eating Index (DHDI 2015) at months 0, 3 and 6[32]. Self-reported self-efficacy for aspects of the program was assessed based on questions 1–9 of the subjective compliance and effort questionnaire evaluated on months 0, 3 and 6 (7 points Likert scale; see Supplementary Materials). Finally, maintenance of lifestyle behaviour change was evaluated based on question 16 related to diet, question 17 related to physical activity and question 22 related to maintaining your own goal from the subjective compliance and effort questionnaire (7-points Likert scale; see Supplementary Materials). Objective assessment of the amount of physical activity was done at baseline, t = 3 and t = 6 months, based on the SQUASH questionnaire[44]. During analysis of the results, it appeared that the SQUASH questionnaires for the intervention and control groups differed on one crucial item. This made it impossible to use the SQUASH algorithm to reliably compare amount and intensity of physical activity between the groups. Therefore, these results are not presented here.

Quality of life and appreciation of combined lifestyle intervention program

Quality of life was assessed using the EQ-5D questionnaire at months 0, 3 and 6. Overall appreciation, as well as appreciation for diverse specific aspects of the program was evaluated at 6 months using a scale from 1 to 10 (question 1) and a 7-points Likert scale (questions 2–13 of the appreciation questionnaire), respectively (see Supplementary Materials).

Anthropometry and blood pressure measurements

At the test day, anthropometrics was executed, including blood pressure (Medisana MTX) measurements and body weight and body composition measurements using the InBody770 (InBody Co., Ltd., Korea). Length, waist and hip circumference were measured using a measuring tape according to standard operating procedures[45].

Measurement of biomarkers

To assess changes in metabolism, multiple clinical chemistry biomarkers including concentrations of glucose, insulin, glycated hemoglobin (HbA1c), total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides (TG), creatinine, albumin, estimated glomerular filtration rate (eGFR), alkaline phosphatase (AF), gamma-glutamyl transferase (GGT), alanine transaminase (ALAT) and aspartate transaminase (ASAT) were quantified in plasma. These lab analyses were performed at the accredited central diagnostic laboratory of University Medical Center Utrecht according to standard operating procedures. Furthermore, plasma biomarkers related to inflammation were measured and included the cytokines interleukin 6 (IL-6), tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) (MesoScale Discovery 'human proinflammatory panel I', Rockville, Maryland, USA) as well as resistin (DY1359), leptin (DY398), adiponectin (DY1065), high-sensitive C-reactive protein (hsCRP; DY1707), IFN-γ-induced protein 10 (IP-10; DIP100), myeloperoxidase (MPO; DY3174), E-selectin (DY724), serpin A1/alpha-1-antitrypsin (AAT; DY1268), haptoglobin (DY8465-05) and serum amyloid A1 (SAA; DY3019) as measured by ELISAs (with antibody sets from R&D Systems, Abingdon, UK). The cytokines (MSD analytes) were measured by electrochemiluminescence according to the protocol for validated multiplex panels (V-plex human proinflammatory panel I) of the manufacturer (MesoScale Discovery, RockVille, Maryland, USA).The manufacturer validates the V-plex panels following a standardized procedure and the coefficient of variation were all below 20% as reported by the manufacturer online for each batch. The ELISAs for the other analytes were validated prior to use in three ways: (1) the linearity of the assay was tested using several dilutions of the protein (biomarker) in question; (2) antigen retrieval was tested by spiking the biomarker in question into plasma and recovery had to be > 80%; (3) the dilution of the biomarker in question was optimized in scouting experiments prior to analysis of the actual study samples to ensure measurement in the linear part of the calibration curve. For the latter, we used pools of the samples from this study. In addition to all the above, optimal performance of all assays (MSD multiplex and ELISAs) used herein was confirmed by analysis of at least one cohort study (in-house studies) prior to use of the assays herein.

Sample size

The primary outcome of the advice is adherence to the lifestyle advice through subjective and objective evaluation. The hypothesis was that personalisation would affect this adherence. Based upon the study of Doets et al.[46] where adherence to advice was also assessed through subjective and objective evaluation in a so called score for implementation intentions on a 7-points Likert scale this was used for sample size calculations. Sample size was calculated using a significance level of 0.05, tested 2-sided giving $Z\alpha = 1.96$; a power of 80%; $1-\beta = 0.80$ giving $Z\beta = 0.842$; the expected deviation (as a measure of variance or distribution) is $\sigma = 1$. The expected effect, being the difference in compliance between intervention and control, $\delta = 0.6$ (based upon scores reported in Table 3 from the study of Doets et al.[46]:

$$\frac{(Z\alpha\ + Z\beta\ )^2 \bullet\ \ \sigma^2}{\delta^2} \bullet 2 = \frac{(1.96 + 0.842)^2 \bullet 1^2}{0.6^2} \bullet 2 = 44\ subjects\ per\ condition$$

Taking into account possible dropouts, $n = 60$ subjects were recruited for each arm.

Statistical analysis

Statistical analyses were done according to the modified intention-to-treat principle, in which participants were included from whom > 80% of baseline data was available, with p-values < 0.05 as statistically significant.

Exploratory factor analysis was used to determine self-efficacy for the followed programs (based on questions 1–9 from subjective compliance and effort questionnaire, see Supplementary Materials). Scree plots, eigenvalues and parallel analysis all suggested the use of two factors. Exploratory factor analysis revealed that outcomes from the self-efficacy questions related to diet and related to physical activity were highly related. Chronbach's alpha for items related to diet was 0.91, and Chronbach's alpha for items on physical activity was 0.92. Self-efficacy factors for diet and for physical activity respectively were calculated by taking the mean of items with factor scores larger than 0.3. These two self-efficacy factors were used for statistical analysis with linear mixed-effects models.

Linear mixed-effects models were fitted to assess changes over time between the intervention and control groups using the *lmerTest* package in R[47]. For each outcome variable, two models were constructed. The default model included fixed effects for timepoint (baseline and follow-up), group (intervention and control), and a random intercept for participant to account for within-subject correlation. The covariate model included the same structure but additionally adjusted for baseline levels of HbA1c and fasting glucose. The response variable in all models was the natural logarithm of the original measurement to stabilize variance and normalize residuals, and all hypothesis tests and model comparisons were performed on this transformed scale. Estimated marginal means and contrasts were subsequently back-transformed to the original response scale to aid interpretation.

Model comparisons between the default and covariate models were performed using maximum likelihood estimation and evaluated with Analysis of Variance (ANOVA). The covariate model was retained when the inclusion of HbA1c and glucose significantly improved model fit, as indicated by a p-value ≤ 0.05. In most cases, the default model was selected; however, for certain outcomes such as body weight, body mass index (BMI), body fat percentage, triglycerides (TG), estimated glomerular filtration rate (eGFR), E-selectin, self-efficacy for physical activity, self-efficacy for diet, the dietary health diet index (DHDI), and health-related quality of life (EQ-5D), the covariate model provided a better fit and was therefore used. For HbA1c and fasting glucose themselves, only the default model was applied, as these variables were used as covariates in other models.

To reduce the influence of extreme values, observations with absolute standardized residuals greater than 3 were excluded from the final model fitting. No imputation was performed.

The interaction between timepoint and group was assessed by including a timepoint-by-group interaction term in the mixed-effects model. This term tested whether the change from baseline to follow-up differed significantly between the intervention and control groups. The significance of the interaction term was evaluated as part of the fixed effects summary of the model. Estimated marginal means (EMMs) were used to further explore the pattern of results. These EMMs, derived from the final model, represented the model-predicted means for each group and timepoint combination on the response scale. Contrasts based on these EMMs were calculated to examine within-group changes over time, between-group differences at each timepoint, and differences in change between groups, thereby providing a detailed decomposition of the interaction effect. All contrasts and estimated means were based on the fixed effects of the model and averaged over random effects. Standard errors, confidence intervals, and model-based estimates of variability were extracted to support interpretation and reporting of results.

Wilcoxon tests were performed for inflammatory biomarkers that did not meet the criteria for using linear mixed-effects models to assess differences between groups and timepoints, using the *rstatix* package[48]. Three different comparisons were made[1]: changes in inflammatory biomarkers were calculated for each participant by subtracting baseline values from follow-up values. Cases with missing values were excluded from further analysis. Wilcoxon tests were then applied to change in values to compare different groups[2]. Paired Wilcoxon tests were used to compare values between the two timepoints within each group[3]. Unpaired Wilcoxon tests were utilized to compare values between different groups at each timepoint. Finally, appreciation question outcomes were analysed using two-sided Student's T-test, since data were only available at the 6 months timepoint.

Data availability

The datasets presented in this publication are available upon reasonable request. Requests to access the datasets should be directed to the corresponding author. The data are being stored in the phenotype database (https://dashin.eu/interventionstudies/), which is a data repository for clinical studies that makes use of ontologies and the principles of F.A.I.R (findable, accessible, interoperable and reusable) to allow for reuse of data.

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Declarations

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The authors declare no competing interests.

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