Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial

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Summary

Background Type 2 diabetes is affecting people at an increasingly younger age, particularly in the Middle East and in north Africa. We aimed to assess whether an intensive lifestyle intervention would lead to significant weight loss and improved glycaemia in young individuals with early diabetes.

Methods This open-label, parallel-group, randomised controlled trial (DIADEM-I), done in primary care and community settings in Qatar, compared the effects of an intensive lifestyle intervention with usual medical care on weight loss and glycaemic outcomes in individuals with type 2 diabetes, aged 18–50 years, with a short diabetes duration (≤3 years), had a BMI of 27·0 kg/m² or more, and who were from the Middle East and north Africa region. Participants were randomly allocated (1:1) either to the intensive lifestyle intervention group or the usual medical care control group by a computer-generated sequence and an online randomisation service. The intensive lifestyle intervention comprised a total diet replacement phase, in which participants were given formula low-energy diet meal replacement products followed by gradual food reintroduction combined with physical activity support, and a weight-loss maintenance phase, involving structured lifestyle support. Participants in the control group received usual diabetes care, which was based on clinical guidelines. The primary outcome was weight loss at 12 months after receiving the assigned intervention. Our analysis was based on the intention-to-treat principle. Key secondary outcomes included diabetes control and remission. The trial was registered with the ISRCTN registry, ISRCTN20754766, and ClinicalTrials.gov, NCT03225339.

Findings Between July 16, 2017, and Sept 30, 2018, we enrolled and randomly assigned 158 participants (n=79 in each group) to the study. 147 participants (70 in the intervention group and 77 in the control group) were included in the final intention-to-treat analysis population. Between baseline and 12 months, the mean bodyweight of participants in the intervention group reduced by 11·98 kg (95% CI 9·72 to 14·23) compared with 3·98 kg (2·78 to 5·18) in the control group (adjusted mean difference –6·08 kg [95% CI –8·37 to –3·79], p<0·0001). In the intervention group, 21% of participants achieved more than 15% weight loss between baseline and 12 months compared with 1% of participants in the control group (p<0·0001). Diabetes remission occurred in 61% of participants in the intervention group compared with 12% of those in the control group (odds ratio [OR] 12·03 [95% CI 5·17 to 28·03], p<0·0001). 33% of participants in the intervention group had normoglycaemia compared with 4% of participants in the control group (OR 12·07 [3·43 to 42·45], p<0·0001). Five serious adverse events were reported in four participants in the control group; four admissions to hospital because of unanticipated events (supraventricular tachycardia, abdominal pain, pneumonia, and epididymo-orchitis), and one admission to hospital for an anticipanted event (hyperglycaemia).

Interpretation Our findings show that the intensive lifestyle intervention led to significant weight loss at 12 months, and was associated with diabetes remission in over 60% of participants and normoglycaemia in over 30% of participants. The provision of this lifestyle intervention could allow a large proportion of young individuals with early diabetes to achieve improvements in key cardiometabolic outcomes, with potential long-term benefits for health and wellbeing.

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Introduction

The prevalence of type 2 diabetes is increasing worldwide, creating a major global health challenge.[1] Type 2 diabetes is associated with serious complications that contribute to reduced quality of life and increased mortality. Over time, an increasing number of young individuals (ie, those aged 18–50 years) are being affected by type 2 diabetes, and these individuals have earlier and more severe diabetes-related complications and reduced longevity.[2] Current recommendations for diabetes management focus strongly on the use of medications to control blood glucose, blood lipids, and blood pressure.[3]

Research in context

Evidence before this study

We searched PubMed from inception to December, 2019, for clinical trials of dietary interventions for weight loss in type 2 diabetes done in the Middle East and north Africa region, where there is a high prevalence of obesity and diabetes. Search terms included: "diet", "Middle East", "North Africa", "diabetes", and "clinical trial" amongst more specific terms that included individual diet and country names. We identified six studies, but most of these were short-term studies and they did not show significant weight loss in the dietary intervention groups. Additionally, none of these studies reported on diabetes remission. Of studies done outside the Middle East and north Africa region, one randomised controlled trial (DiRECT) done in the UK reported in 2018 that diabetes remission occurred in about half of participants who achieved significant weight loss through total diet replacement (formula low-energy diet meal replacement products followed by stepped food reintroduction). The generalisability of these findings to all patients with type 2 diabetes, however, remains to be established.

Added value of this study

To our knowledge, the DIADEM-I study is the first randomised controlled clinical trial of an intensive lifestyle intervention, involving a total diet replacement phase (low-energy meal replacement formula diet products) followed by gradual food reintroduction, in individuals with type 2 diabetes from the Middle East and north Africa region. Compared with previous studies, our study included participants who were younger and had a shorter duration of diabetes, and included a greater proportion of men.

Implications of all the available evidence

The DIADEM-I study showed that young (aged 18–50 years) individuals with early type 2 diabetes (diabetes duration of 3 years or less) were able to achieve significant weight loss, resulting in diabetes remission and normoglycaemia in a greater proportion of participants than has been observed in previous studies. Offering this intervention to younger patients at the earliest opportunity is likely to reduce the burden of diabetes and its associated complications.

However, this approach results in a substantial patient burden and health-care costs.

Insufficient focus has been placed on addressing the underlying reversible causes of diabetes. This notion is reinforced by the view that type 2 diabetes is irreversible and requires drug treatment escalation to manage increasing insulin resistance and progressive pancreatic β-cell dysfunction.[4] Observations from studies[5–8] of bariatric surgery and dietary energy restriction, however, have challenged this view, by showing that energy restriction and significant weight loss result in improved glycaemic control, a reduction in diabetes medications and diabetes remission. Achieving diabetes remission after bariatric surgery correlates with the degree of weight loss, a younger age, shorter diabetes duration, and the use of a lower number of diabetes medications before surgery.[9,10] In the DiRECT study,[7] 46% of participants with type 2 diabetes who underwent a dietary intervention (total diet replacement with formula low-energy diet meal replacement products) in primary care achieved diabetes remission in a cost-effective manner. At 2 year follow-up, over a third of participants in the dietary intervention group remained in remission.[11] The generalisability of the DiRECT study results to other populations, however, remains to be elucidated.

The prevalence of obesity and diabetes in the Middle East and north Africa is high, and these conditions affect individuals from a younger age than in white European populations.[12] We did the Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) trial, which is the first randomised controlled trial in young patients with early diabetes (duration of 3 years or less) in primary care and who are from the Middle East and north Africa region, to examine the effect of a 12-month intensive lifestyle intervention, incorporating a total diet replacement phase (with formula low-energy diet meal replacement products), on weight loss and glycaemic control.[13]

Methods

Study design and participants

The DIADEM-I study was an open-label, parallel-group, randomised controlled trial done in one primary health-care centre and one community health-care centre in Doha (Qatar). The study received ethical approval from the Weill Cornell Medicine-Qatar (WCMQ) Institutional Review Board (15–00071), the Hamad Medical Corporation-Qatar Institutional Review Board (15395_15), the Primary Health Care Corporation-Qatar Institutional Review Board (PHCC/IEC/17/02/002), and the Ministry of Public Health-Qatar. The study was supported by the WCMQ Data and Safety Monitoring Board, which reviews the study every 6 months. The study protocol, including the study rationale, hypothesis, details of recruitment, study interventions, procedures, and conduct, equipment used, biochemical analyses, and planned data analyses have been published previously.[13]

Eligible participants were those who provided written informed consent, were aged 18–50 years, reported a diagnosis of type 2 diabetes within the previous 3 years (as confirmed from available medical records), had a BMI of 27·0 kg/m² or more, originated from the Middle East and north Africa region, and who were resident in Qatar. Individuals were excluded if they: had type 1

diabetes, had had an ischaemic cardiovascular event in the previous 6 months, had stage 3b or higher chronic kidney disease, were pregnant, lactating, or planning a pregnancy, had any condition precipitating fluid overload, such as heart failure or liver cirrhosis, had been diagnosed with a severe psychiatric disorder, had uncontrolled depression, had uncontrolled epilepsy, had known lactose intolerance, had severe arthritis that prevented walking, had active gout, or had active gallstone disease or known asymptomatic gallstones.

Randomisation and masking

Randomisation was done by use of a computer-generated sequence with variable blocks of two, four, and six. Clinical research coordinators randomly assigned (1:1) eligible participants to receive either the intensive lifestyle intervention or usual medical care. Allocations were done in Stata 13.1 by the trial statistician and were programmed into an online randomisation service. Once recruited, participants were given a study identification number. A study coordinator accessed the online randomisation service, and after the participant's eligibility criteria were entered, the allocation was provided. Because of the nature of the interventions, masking of participants and investigators was not possible. However, the trial statistician was masked to the study groups during data analysis.

Procedures

Potentially eligible participants were identified by the clinical primary care team from electronic medical records, and were referred to the study. After providing written informed consent, the final eligibility of participants was established before they were randomly assigned to either the intensive lifestyle intervention group or the usual medical care control group.

Participants in the intensive lifestyle intervention group were supported by a team of trained dietitians, personal trainers, and physicians, who followed a standard intervention delivery protocol. Participants were not exclusively paired with a specific dietitian, trainer, or physician, and they saw several different members of the team throughout the study. The multidisciplinary team discussed individual participants and their progress, allowing uniformity of the intervention. After randomisation, participants underwent a 12-week total diet replacement phase, in which they were given formula low-energy (800–820 kcal/day) diet meal replacement products (57% carbohydrate, 14% fat, 26% protein, and 3% fibre; Cambridge Weight Plan, Northants, UK), followed by a 12-week structured food reintroduction phase. Thereafter, participants managed their own energy-restricted food intake and lifestyle changes for 6 months. Meal replacement products were provided at no cost. All diabetes medications were discontinued at the start of the intervention. Antihypertensives and lipid-lowering drugs were adjusted or discontinued on the basis of current values for individual participants and clinical judgment. Medications were reintroduced on the basis of clinical and biochemical assessments and followed local clinical guidelines. Eating raw vegetables and salad was permitted in the total diet replacement phase, if required. Participants were advised to drink 2 L or more of water daily. If required, a fibre supplement was recommended for constipation. In the total diet replacement and food reintroduction phases, participants were seen by dietitians and personal trainers once every 2 weeks. Thereafter, participants attended the intervention clinic once per month. When food was reintroduced, a regular meal pattern with a similar distribution of macronutrients as the meal replacement products was recommended. Participants were advised to aim for low-glycaemic index carbohydrates. Physical activity support initially focused on walking (with an aim of at least 10 000 steps per day), followed by the recommendation of increasing unsupervised activity to at least 150 min/week.[13] Participants were provided with a wrist-worn accelerometer and were directed to smartphone apps to monitor food intake and activity; however, the data uploaded to these apps were not used in the study. The behavioural modification aspects of the study have been described elsewhere.[13,14] Participants were seen by a physician at baseline and then once every 3 months thereafter.

For more on the **online randomisation service** see https://www.sealedenvelope.com

Participants in the control group received usual medical diabetes care according to clinical guidelines.[15] Adjustments to medication were made to aid individualised glycaemic, lipid, and blood pressure control, and to facilitate weight loss or weight maintenance. Standard diet and activity advice, and diabetes education were provided. Participants were seen by a physician at baseline and then once every 3 months thereafter. Participants had access to diabetes educators and dietitians in both primary and secondary care.

Outcomes

All study procedures, outcome measures, and the frequency of assessments have been described previously.[13] The primary outcome was weight loss at 12 months after commencing the intervention. Secondary outcomes included improved glycaemic control and diabetes remission. Diabetes remission was defined as: HbA_{1c} values of less than 6·5% (<48 mmol/mol), and receiving no pharmacological therapy for diabetes for at least 3 months. Normoglycaemia was defined as: HbA_{1c} values of less than 5·7% (<39 mmol/mol), and receiving no pharmacological therapy for diabetes for at least 3 months.

Other prespecified outcomes of interest included anthropometric measures and body composition measurements (bioimpedance, measured by use of the Tanita BC-420MA body composition analyser [Tanita, Amsterdam, Netherlands]), blood pressure, blood lipids, and insulin sensitivity, as measured by use of the quantitative insulin-sensitivity check index (QUICKI) and the homeostatic model assessment index for insulin

resistance (HOMA-IR).[13] Measures of glucose variability were assessed by interstitial continuous glucose monitoring for 7 days with the iPro2 continuous glucose monitor (Medtronic, Northridge, CA, USA). Quality of life was assessed by use of the generic EuroQol 5 Dimensions (EQ-5D) questionnaire, and the weight-specific impact of weight on quality of life-lite (IWQoL-Lite) questionnaire.[13] Self-reported physical activity was assessed by use of the short-form International Physical Activity Questionnaire (IPAQ).[13] Anxiety and depression were assessed by use of the Hospital Anxiety and Depression Scale.[13]

Statistical analysis

Sample size calculations were based on the number of participants needed to have 80% power at a 0·05 significance level to test the primary hypothesis. The primary outcome was weight loss at 12 months. We anticipated that participants in the intervention group would lose 7% more weight than those in the control group at 12 months.[16,17] The Look AHEAD trial[17] yielded a conservative estimate of the SD of the percentage of weight loss to be 9%. Using the ANCOVA method, we specified the correlation between baseline and 12 months as 0·5 and calculated that 69 participants in each group needed to be recruited to detect a 7% difference in weight after 12 months, allowing for 30% dropout. Regarding glycaemic control, the Look AHEAD intensive lifestyle intervention trial[17] reported a change in HbA_{1c} of –0·64% (SD 0·99).[17] A 0·5% reduction in HbA_{1c}, however, is considered to be clinically significant and similar to that attained with most diabetes medications. Enrolling 69 participants per group was also sufficient to detect a 0·5% change in HbA_{1c} (assuming an SD of 1%, 80% power, a significance level of 0·05, and that 30% of participants would drop out). Therefore, we aimed to recruit a total of 138 individuals (69 individuals in each group), assuming that 30% of participants would drop out.

Prespecified primary statistical analyses were done at the participant level and followed the intention-to-treat principle. Outcomes of weight loss, glycaemic control, remission of diabetes, and improved quality of life were analysed in separate between-group regression models, with no adjustment for multiple comparisons. To provide comparability with other published data for weight changes, we did a sensitivity analysis with different missing data imputation models and statistical analysis methods (appendix p 2). Outcomes and the changes from baseline were compared by use of between-group regression models with adjustments for age, sex, baseline BMI, and baseline outcome value. Logistic models were used for binary outcomes and parametric models were used for continuous outcomes. For continuous outcomes, model fit was assessed visually with normal probability plots. When a departure from a normal distribution was observed, Mann-Whitney-Wilcoxon tests were applied. For binary outcomes, we used Fisher's exact test to compare the groups. Significance tests were based on least-squares means using a two-sided α value of 0·05 (two-sided 95% CIs). Analyses were done by use of Stata-MP 15 (with regression and logit commands). The primary treatment comparison was the difference from baseline between the intensive lifestyle intervention and usual care at the endpoint visit.

See Online for appendix

This trial is registered with the ISRCTN registry, ISRCTN20754766, and ClinicalTrials.gov, NCT03225339.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 16, 2017, and Sept 30, 2018, 1498 potential participants were identified from primary care electronic medical records and were screened by primary care staff (figure 1). 267 (17·8%) of these individuals were referred into the study and considered as potentially eligible, and they were scheduled to attend a study consent visit (figure 1). 209 (78%) of these 267 individuals provided consent to participate in the study; 36 of whom were found to be ineligible and 15 withdrew before randomisation. A total of 158 participants were enrolled and randomly assigned to the intensive lifestyle intervention group (n=79) or the control group (n=79). A total of 147 participants were included in the final intention-to-treat analysis (figure 1). As specified in the trial protocol, 18 individuals were recruited to replace participants who withdrew early (ie, within 6 weeks of commencing the intervention) in the study.[13] In the intensive lifestyle intervention group, eight participants withdrew during the total diet replacement phase, two withdrew during the food reintroduction phase, and five withdrew in the maintenance phase (figure 1), resulting in a total of 21% of participants withdrawing from this group, with 53% of withdrawals occurring in the first phase of the study. The intensive lifestyle intervention was well attended, with 67% of all possible visits attended by participants. The same proportion of participants in the intervention and control groups (82%) attended physician visits. One participant in the intervention group had significant weight loss between baseline and 12 months (16·9 kg), but had deteriorating glycaemic control, and was subsequently diagnosed with insulin-dependent diabetes with positive autoantibodies. Data from this participant were excluded from the final analysis.

Baseline characteristics were similar between the two groups (table 1). For all participants, mean age was 42·1 years (SD 5·6) and BMI was 34·9 kg/m² (5·5). The majority of participants were male (73%). Mean diabetes

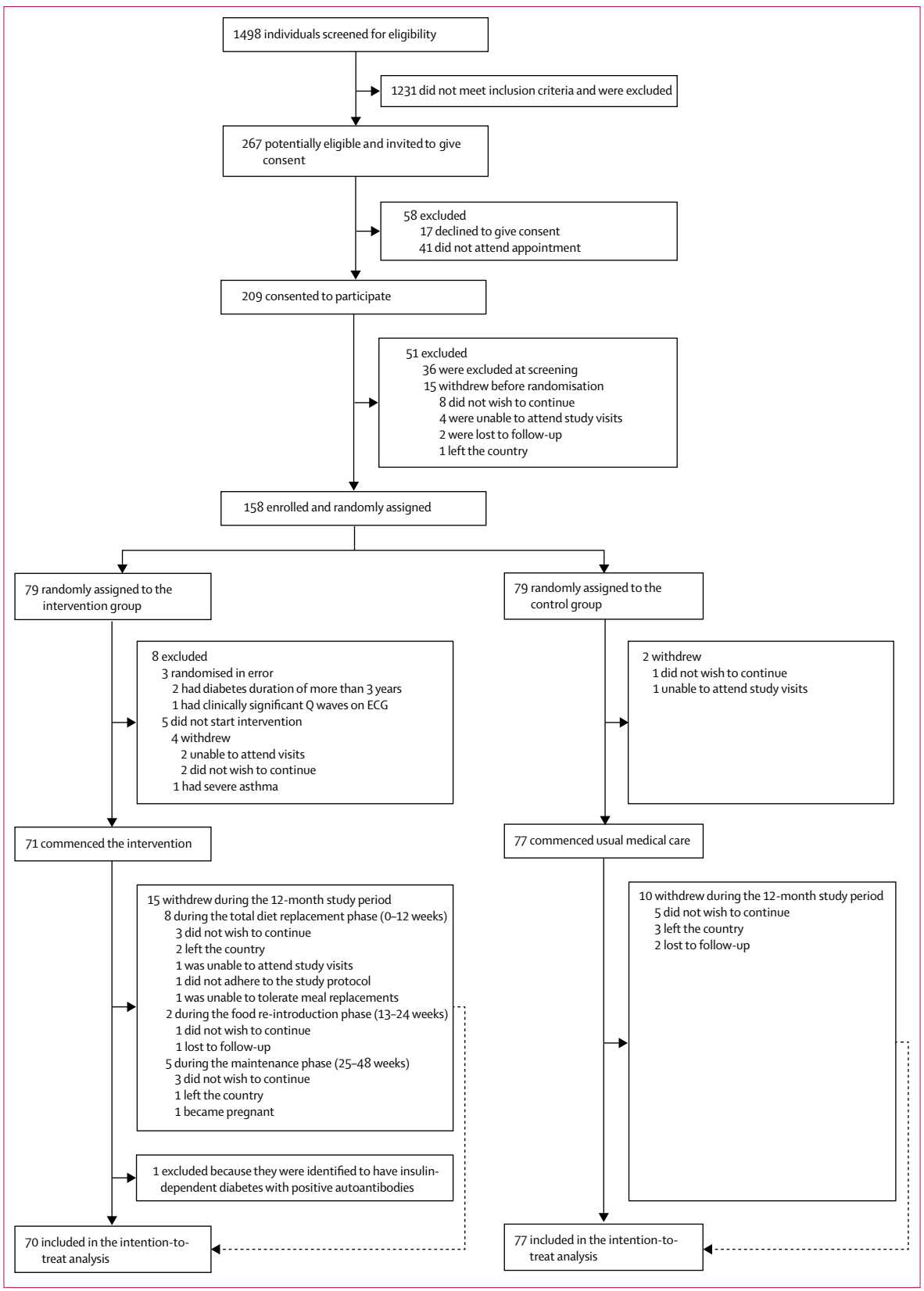


Figure 1. Trial profile
ECG=electrocardiogram.

	Lifestyle intervention group (n=70)	Usual medical care control group (n=77)
Male	49 (70%)	58 (75%)
Female	21 (30%)	19 (25%)
Age, years	41·9 (5·4)	42·3 (5·8)
Bodyweight, kg	100·6 (19·5)	101·7 (19·3)
BMI, kg/m²	35·0 (5·2)	34·8 (5·8)
Waist circumference, cm	113·2 (12·5)	113·2 (12·8)
Fat mass, kg	37·9 (12·3)	37·1 (13·9)
Lean mass, kg	59·6 (9·4)	61·3 (10·4)
Duration of diabetes, months	21·9 (11·5)	20·5 (13·0)
Number of diabetes medications		
0	6 (8·6%)	9 (11·7%)
1	35 (50%)	28 (36·4%)
2	19 (27·1%)	25 (32·5%)
≥3	10 (14·3%)	15 (19·5%)
Type of treatment or diabetes medication		
Diet	6 (8·6%)	9 (11·7%)
Metformin	61 (87·1%)	68 (88·3%)
Sulfonylurea	15 (21·4%)	22 (28·6%)
DPP-4 inhibitor	22 (31·4%)	27 (35·1%)
Thiazolidinedione	2 (2·9%)	2 (2·6%)
SGLT2 inhibitor	3 (4·3%)	4 (5·2%)
GLP-1 receptor agonist	2 (2·9%)	1 (1·3%)
Insulin	1 (1·4%)	0
HbA_{1c}	6·95% (1·40)	6·95% (1·22)
HbA_{1c}, mmol/mol*	52·5 (15·3)	52·5 (13·3)
Fasting blood glucose concentration, mmol/L	7·5 (2·3)	7·5 (2·1)
Quantitative insulin sensitivity check index	0·2 (0·03)	0·2 (0·03)
Homeostatic model assessment index-insulin resistance	2·1 (1·7)	2·2 (1·4)
Systolic blood pressure, mm Hg	131·1 (14·6)	128·8 (13·4)
Diastolic blood pressure, mm Hg	83·7 (8·9)	82·9 (9·3)
Heart rate, beats per min	77·7 (10·4)	78·2 (10·4)
Hypertension	22 (32·4%)	22 (28·6%)
Number of antihypertensive medications		
0	46 (65·7%)	55 (71·4%)
1	15 (21·4%)	12 (15·6%)
2	7 (10%)	7 (9·1%)
3	2 (2·9%)	3 (3·9%)
Cardiovascular disease	1 (1·4%)	0
Total cholesterol, mmol/L	4·9 (1·0)	4·6 (0·9)
HDL cholesterol, mmol/L	1·1 (0·4)	1·0 (0·2)
Triglycerides, mmol/L	1·7 (1·1–2·3)	1·7 (1·2–2·5)
Statins	21 (30%)	29 (37·7%)
Other lipid-lowering medications	5 (7·1%)	4 (5·2%)
Albumin-to-creatinine ratio, mg/mmol	5·0 (9·0)	3·1 (5·2)
Estimated glomerular filtration rate, mL/min per 1·73 m²†	114·2 (22·2)	110·6 (23·5)
One or more diabetes-related microvascular complications	4 (5·7%)	2 (2·6%)
Current smoker	16 (22·9%)	18 (23·4%)
EQ-5D scale score	79·9 (19·4)	82·0 (15·1)
IWQoL-Lite score	91·2 (11·5)	89·1 (17·5)
Time spent sitting, min/day‡	442·9 (207·0)	452·0 (233·7)

Data are n (%), mean (SD), median (IQR), unless otherwise indicated. EQ-5D=EuroQol 5 Dimensions. IWQoL-Lite=impact of weight on quality of life-lite. *Reported as International Federation of Clinical Chemistry units. †According to the Modification of Diet in Renal Disease Study equation. ‡According to the International Physical Activity Questionnaire.

Table 1: **Baseline characteristics**

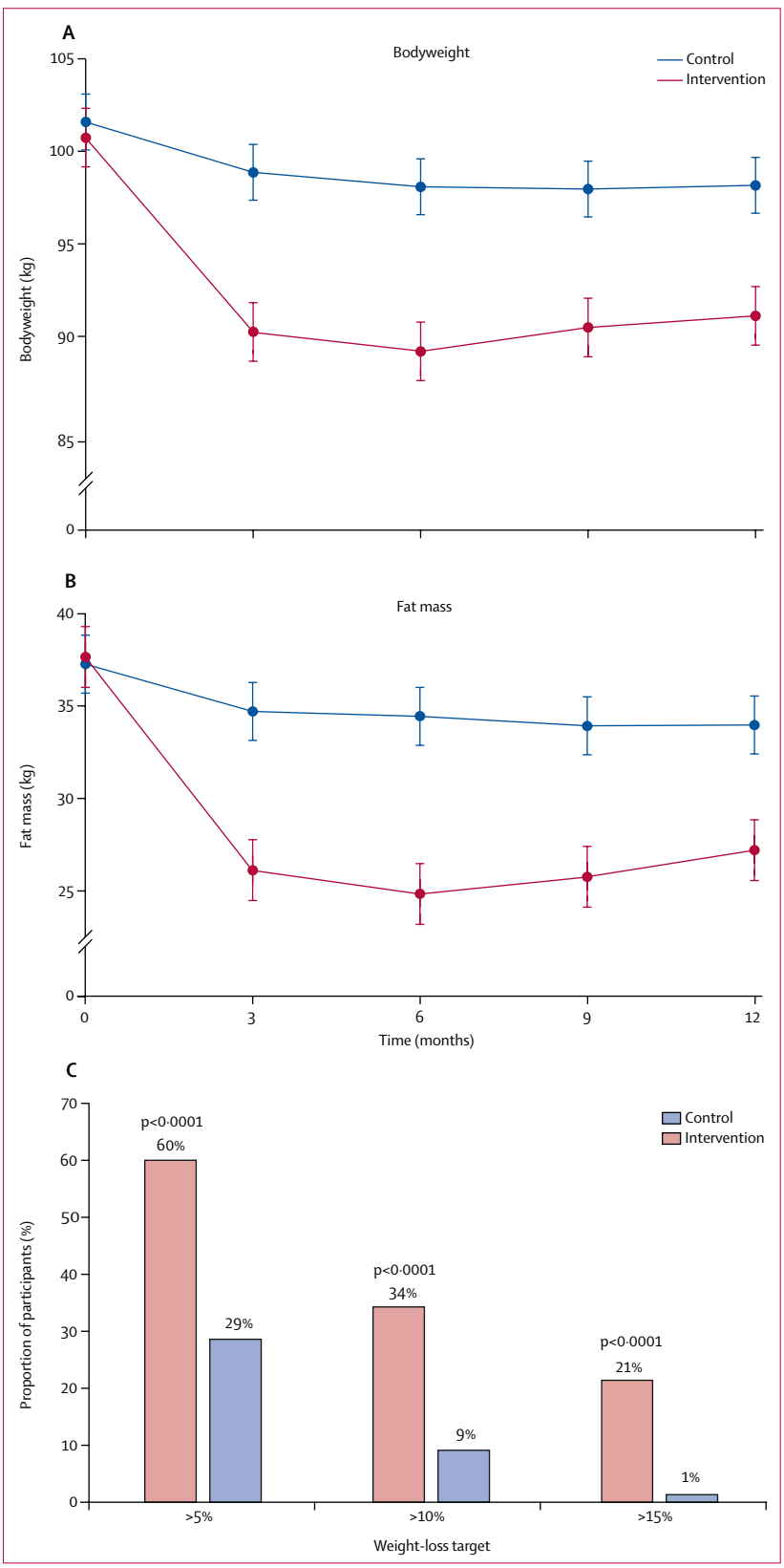
duration was 21·2 months (12·3). 15 (10%) participants had been managing their diabetes with diet alone. Mean HbA_{1c} was 7·0% (SD 1·3; 52·5 mmol/mol [SD 14·3]). No participant had a reported history of diabetic retinopathy or neuropathy, but six (4%) participants had a history of diabetic nephropathy. However, according to albumin-to-creatinine ratios, 40 (29%) of 138 participants had microalbuminuria (18 [29%] of 63 participants in the intervention group, and 22 [29%] of 75 participants in the control group). A third of all 147 participants reported a history of hypertension. Mean systolic blood pressure was 129·8 mm Hg (SD 14) and mean diastolic blood pressure was 83·3 mm Hg (9·1). Mean total cholesterol was 4·7 mmol/L (1·0), and 50 (34%) of all participants were taking statins. Only one (0·7%) participant had a history of previous atherosclerotic heart disease. Five (3%) participants reported a previous diagnosis of non-alcoholic fatty liver disease, and ten (7%) participants had undergone a cholecystectomy. 34 (23%) participants were current smokers. Quality of life scores were high, and participants reported being sedentary (mean length of time sitting was 447·7 min per day [SD 220·5]).

Between baseline and 12 months, the mean reduction in bodyweight of participants was 11·98 kg (95% CI 9·72 to 14·23; SD 9·46) in the intervention group and 3·98 kg (2·78 to 5·18; 5·29) in the control group (adjusted difference –6·08 kg [95% CI –8·37 to –3·79], p<0·0001; table 2). Sensitivity analyses using alternative assumptions for missing data resulted in similar findings (appendix p 2). In the intervention group, the greatest reduction in weight occurred between baseline and 3 months (during the total diet replacement phase), followed by a slower but continued reduction in weight between 3 and 6 months (figure 2A). After this point, weight loss was maintained until 12 months. The

	n	Mean (SD)			Intervention effect		
		Baseline	12 months	Change	Estimate (SE)	95% CI	p value
Weight, kg	..	..	..	..	−6·08 (1·16)	−8·37 to −3·79	<0·0001
Intervention	70	100·64 (16·95)	90·30 (16·85)	−11·98 (9·46)	..	..	..
Control	77	101·68 (19·26)	96·85 (17·13)	−3·98 (5·29)	..	..	..
Waist circumference, cm	..	..	..	..	−6·97 (1·45)	−9·86 to −4·10	<0·0001
Intervention	69	113·21 (12·45)	102·87 (14·04)	−11·44 (9·90)	..	..	..
Control	77	113·24 (12·78)	108·40 (11·73)	−4·03 (5·68)	..	..	..
Waist-to-hip ratio	..	..	..	..	−0·06 (0·01)	−0·08 to −0·04	<0·0001
Intervention	69	0·96 (0·09)	0·87 (0·09)	−0·10 (0·08)	..	..	..
Control	77	0·96 (0·07)	0·93 (0·08)	−0·03 (0·05)	..	..	..
Fat mass, kg	..	..	..	..	−5·43 (1·19)	−7·81 to −3·06	<0·0001
Intervention	70	37·94 (12·33)	28·51 (12·09)	−9·97 (9·06)	..	..	..
Control	77	37·13 (13·94)	33·13 (12·47)	−2·89 (6·41)	..	..	..
Lean mass, kg	..	..	..	..	−0·26 (1·19)	−1·16 to 0·65	0·579
Intervention	70	59·56 (9·44)	58·15 (9·64)	−1·41 (2·92)	..	..	..
Control	77	61·34 (10·35)	60·00 (9·58)	−1·33 (2·94)	..	..	..
HbA_{1c}	..	..	..	..	−0·62 (0·46)	−0·92 to −0·33	0·020
Intervention	67	6·95% (1·40)	5·96% (0·84)	−0·89% (1·05)	..	..	..
Control	75	6·95% (1·22)	6·59% (0·92)	−0·35% (1·27)	..	..	..
HbA_{1c}, mmol/mol	..	..	..	..	−6·77 (1·68)	−10·09 to −3·46	0·020
Intervention	67	52·48 (15·29)	41·59 (9·12)	−9·50 (11·31)	..	..	..
Control	75	52·51 (13·28)	48·78 (10·29)	−3·46 (14·70)	..	..	..
Number of diabetes medications	..	..	..	..	−1·54 (0·15)	−1·84 to −1·24	<0·0001
Intervention	68	1·52 (0·99)	0·13 (0·54)	−1·38 (1·03)	..	..	..
Control	77	1·61 (0·96)	1·79 (1·15)	0·06 (1·19)	..	..	..
Systolic blood pressure, mm Hg	..	..	..	..	−0·36 (1·66)	−3·63 to 2·92	0·827
Intervention	68	131·09 (14·62)	124·72 (11·94)	−8·19 (12·66)	..	..	..
Control	77	128·77 (13·42)	123·91 (10·31)	−4·42 (11·44)	..	..	..
Diastolic blood pressure, mm Hg	..	..	..	..	−1·49 (1·10)	−3·68 to 0·68	0·177
Intervention	68	83·72 (8·94)	79·53 (8·37)	−5·60 (7·34)	..	..	..
Control	77	82·92 (9·25)	80·41 (8·85)	−2·24 (7·88)	..	..	..
Number of antihypertensive medications	..	..	..	..	−0·36 (0·11)	−0·58 to −0·14	0·002
Intervention	68	0·53 (0·90)	0·31 (0·80)	−0·24 (0·84)	..	..	..
Control	77	0·45 (0·81)	0·62 (1·01)	0·15 (0·54)	..	..	..
Total cholesterol, mmol/L	..	..	..	..	0·86 (0·17)	0·52 to 1·18	<0·0001
Intervention	67	4·89 (1·02)	5·15 (1·04)	0·23 (1·21)	..	..	..
Control	77	4·60 (0·93)	4·22 (0·94)	−0·43 (1·03)	..	..	..
HDL cholesterol, mmol/L	..	..	..	..	0·08 (0·04)	0·01 to 0·15	0·033
Intervention	67	1·10 (0·40)	1·15 (0·27)	0·03 (0·40)	..	..	..
Control	77	0·97 (0·20)	1·00 (0·23)	0·03 (0·11)	..	..	..
LDL cholesterol, mmol/L	..	..	..	..	0·82 (0·15)	0·51 to 1·13	<0·0001
Intervention	66	3·01 (0·88)	3·29 (0·89)	0·30 (1·10)	..	..	..
Control	77	2·78 (0·86)	2·46 (0·87)	−0·36 (0·94)	..	..	..
Triglycerides, mmol/L	..	..	..	..	−0·02 (0·14)	−0·05 to 0·05	0·098
Intervention	67	1·98 (1·70)	1·71 (1·03)	−0·50 (1·50)	..	..	..
Control	77	1·89 (0·92)	1·58 (0·86)	-0·13 (0·92)	..	..	..
Quality of life*	..	..	..	..	4·03 (2·60)	−1·12 to 9·19	0·124
Intervention	65	79·89 (9·36)	83·81 (11·55)	4·32 (16·80)	..	..	..
Control	72	81·96 (15·11)	80·98 (16·73)	−1·03 (16·51)	..	..	..

Intervention effects reported as estimated mean differences adjusted for age, gender, baseline BMI, and baseline values as fixed effects. *As measured by the EuroQol 5 Dimensions scale.

Table 2: **Key outcomes at 12 months in the analysis population**



reduction in mean waist circumference between baseline and 12 months was significantly greater in the intervention group than in the control group (adjusted difference –6·97 cm [95% CI –9·86 to –4·10], p<0·0001]; table 2). In addition, a significantly greater reduction in mean fat mass between baseline and 12 months was observed in the intervention group compared with the control group (adjusted difference –5·43 [95% CI –7·81 to –3·06], p<0·0001; figure 2B; table 2). The proportion of participants with a recorded weight loss of more than 5%, more than 10%, and more than 15% between baseline and 12 months is reported (figure 2C). 14 (18%) of 77 participants in the control group gained weight between baseline and 12 months, whereas none of the participants in the intervention group gained weight.

The reduction in mean HbA_{1c} between baseline and 12 months was greater in the intervention group than in the control group (adjusted difference –0·62 [95% CI –0·92 to –0·33], p=0·020; table 2; figure 3A). There were improvements in insulin sensitivity variables (QUICKI and HOMA-IR scores; appendix p 3). Participants in both groups took a similar number of diabetes medications at baseline (table 1). In the intervention group, improvements in HbA_{1c} were accompanied by fewer participants taking diabetes medications (four [6%] of 68 participants) compared with the control group (58 [81%] of 72 participants). Diabetes remission occurred in 43 (61%) of 70 participants in the intervention group compared with nine (12%) of 77 participants in the control group (odds ratio [OR] 12·03 [95% CI 5·17–28·03], p<0·0001; figure 3B). Normoglycaemia occurred in 23 (33%) of 70 participants in the intervention group and three (4%) of 77 participants in the control group (12·07 [3·43–42·45], p<0·0001; figure 3B). Several measures of glycaemic control and variability measured through continuous glucose monitoring showed significantly greater improvements in the intervention group compared with the control group (appendix p 4).

The proportion of participants taking antihypertensive medications was similar in the two groups at baseline (table 1). A greater reduction in mean systolic and diastolic blood pressure between baseline and 12 months was observed in the intervention group compared with the control group, but the difference between the two groups was not significant (table 1). However, the proportion of participants taking antihypertensives at 12 months was significantly lower in the intervention group (11 [16%] of 68 participants) than in the control group (25 [35%] of

Figure 2: **Weight and body composition outcomes**
Bodyweight (A) and fat mass (B) over 12 months. Error bars show the 84% CIs. (C) Proportion of participants achieving key weight-loss targets over 12 months. The y-axis shows the proportion of participants who achieved key weight-loss targets (x-axis) between baseline and 12 months in the intervention group and the control group (>5% weight loss, odds ratio 4·5 [95% CI 2·1–9·5]; >10% weight loss, 6·3 [2·4–16·7]; >15% weight loss, 20·7 [2·3–182·9]).

72 participants; p<0·0001). The proportion of participants who were normotensive (defined as a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg, with no antihypertensive medications) at 12 months was significantly higher in the intervention group (50 [71%] of 70 participants) than in the control group (38 [49%] of 77 participants; p=0·007; appendix p 13).

The proportion of participants taking lipid-lowering medications at baseline was 31% (22 of 70 participants) in the intervention group and 40% (31 of 77 participants) in the control group. At 12 months, 18 (26%) of 68 participants in the intervention group and 55 (76%) of 72 participants in the control group were taking lipid-lowering medications (OR 0·11 [95% CI 0·05–0·24], p<0·0001). Mean total cholesterol and mean LDL-cholesterol increased at 12 months in the intervention group but reduced in the control group. Between baseline and 12 months, mean HDL cholesterol increased in both groups, but a greater increase was observed in the intervention group than in the control group (table 2). A greater reduction in mean serum triglycerides was observed in the intervention group compared with the control group, but the difference between the two groups was not significant.

A greater reduction in the total number of medications for all conditions was observed in the intervention group compared with the control group. In the intervention group, participants were taking a mean of 3·5 (SD 1·9) medications (median 3, range 0–8) at baseline and a mean of 2·0 (2·2) medications (1; 0–9) at 12 months. In the control group, participants were taking a mean of 3·6 (1·9) medications (3; 0–9) at baseline and a mean of 4·9 (2·8) medications (5; 0–12) at 12 months. At 12 months, the mean number of medications that participants were taking was significantly lower in the intervention group than in the control group (p<0·0001).

Between baseline and 12 months, patient-reported quality-of-life scores, measured by use of the EQ-5D visual analogue scale, increased in the intervention group but reduced in the control group (adjusted difference 4·03 [95% CI –1·12 to 9·19], p=0·124; table 2). Between baseline and 12 months, IWQoL-Lite scores were increased in the intervention group (12·3 [SD 16·9]) and in the control group (6·6 [13·7]; adjusted difference 3·7 [95% CI –0·9 to 8·3], p=0·103). There was no difference between groups in terms of mental health outcomes at 12 months (appendix p 5).

For physical activity, as measured by use of the IPAQ (appendix p 6), the length of time spent sitting per day between baseline and 12 months was reduced by 40·8 min (SD 260·3) in the intervention group and increased by 68·8 min (191·0) in the control group (adjusted difference –88·1 min [95% CI –162·2 to –14·0], p=0·020; appendix p 6). Mean metabolic equivalent of task (MET)-min/week for walking increased by 151·2 [SD 994·7] in the intervention group but reduced by 235·7 [652·0] in the control group (adjusted difference 410·3 [95% CI 160·3–660·3], p=0·002; appendix p 6). No significant difference in the number of MET-min/week for moderate and vigorous activity, and the total MET-min/week, was observed between the two groups. Between baseline and hs, mean resting heart rate was reduced by 5·1 beats per min (SD 8·3) in the intervention group and reduced by 2·3 beats per min (8·9) in the control group (adjusted difference –3·2 [95% CI –6·1 to –0·4], p=0·03).

Five serious adverse events were reported in four participants in the control group; four admissions to hospital because of unanticipated events (supraventricular tachycardia, abdominal pain, pneumonia, and epididymo-orchitis), and one admission to hospital for an anticipanted event (hyperglycaemia; table 3). Only one

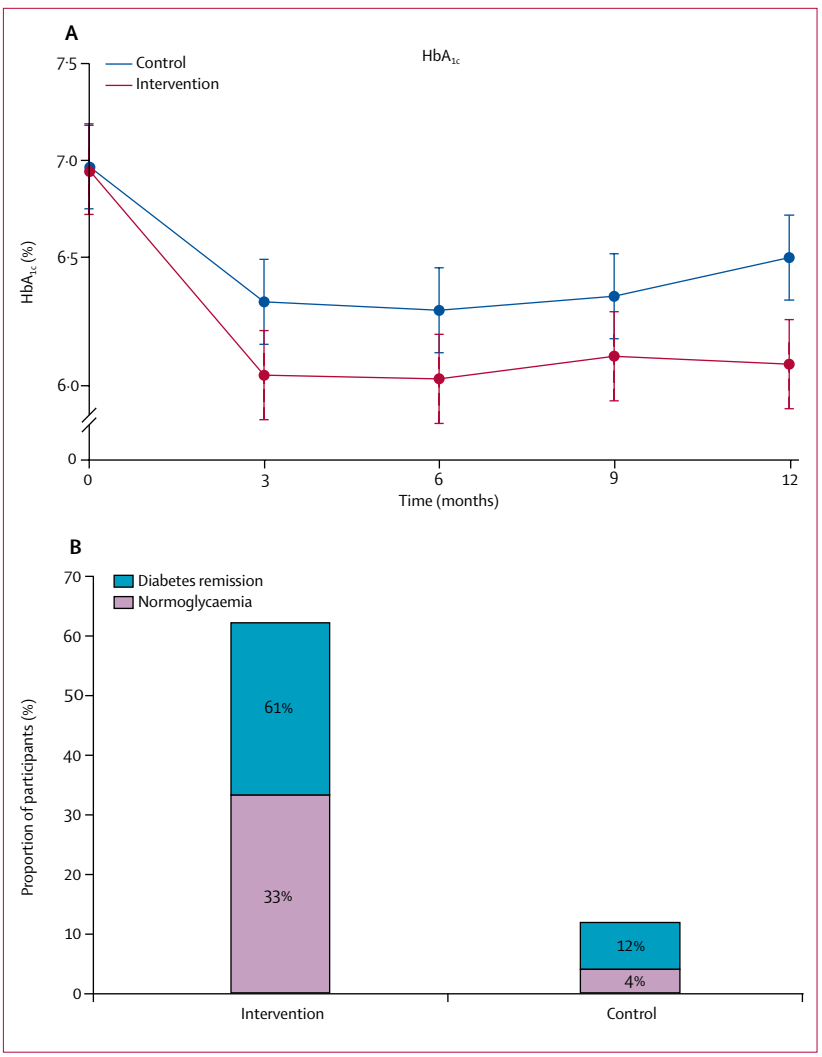


Figure 3: **Glycaemic outcomes**
(A) HbA_{1c} values over 12 months. Error bars show the 84% CIs. (B) Proportion of participants who had diabetes remission (defined as HbA_{1c} <6·5% [<48 mmol/mol] and no medications for 3 months; odds ratio 12·03 [95% CI 5·17–28·03]) and normoglycaemia (defined as HbA_{1c} <5·7% [<39 mmol/mol] and no medications for 3 months; 12·07 [3·43–42·45]) at 12 months.

	All (n=147)	Lifestyle intervention group (n=70)	Usual medical care control group (n=77)
All adverse events			
Number of serious adverse events	5 (3%)	0	5 (6%)
Number of participants with any serious adverse event	4 (3%)	0	4 (5%)
Unanticipated adverse events			
Cardiovascular	1 (<1%)	0	1 (1%)
Arrhythmia*	1 (<1%)	0	1 (1%)
Gastrointestinal	1 (<1%)	0	1 (1%)
Abdominal pain†	1 (<1%)	0	1 (1%)
Respiratory	1 (<1%)	0	1 (1%)
Pneumonia	1 (<1%)	0	1 (1%)
Urological	1 (<1%)	0	1 (1%)
Epididymo-orchitis	1 (<1%)	0	1 (1%)
Anticipated adverse events			
Metabolic	1 (<1%)	0	1 (1%)
Hyperglycaemia	1 (<1%)	0	1 (1%)

Data are n (%). *This participant had known paroxysmal supraventricular tachycardia. †Suspected pancreatitis was excluded.

Table 3: **Serious adverse events**

serious adverse event (hyperglycaemia) was anticipated. All serious adverse events were resolved with appropriate management. Most reported adverse events in the intervention group were mild (appendix pp 7–9). The common adverse events reported in the intervention group were similar to those associated with low-energy diets described previously, and improved after the total diet replacement phase. Compared with the control group, more participants in the intervention group reported dizziness, constipation and other gastrointestinal symptoms, hair loss, and fatigue (appendix pp 10–12). Upper respiratory tract infections were more frequent in the intervention group than in the control group. This difference was most probably associated with increased reporting in the intervention group compared with the control group, as there were more visits in the intervention group than in the control group. A greater number of musculoskeletal adverse events were reported in the intervention group compared with the control group, potentially related to the increase in physical activity in the intervention group.

Discussion

The results of our study indicate that sustained significant weight loss can be achieved through an intensive lifestyle intervention delivered in community and primary care settings to individuals with early type 2 diabetes from the Middle East and north Africa region. The weight loss and lifestyle change were associated with a large proportion of participants having diabetes remission and a third of participants having normoglycaemia at the end of the 12-month follow-up period. There were also benefits associated with most cardiovascular disease risk factors and quality of life. Our findings show that type 2 diabetes is reversible in a significant proportion of patients, provided that the condition is managed early, and they challenge the commonly held view that type 2 diabetes is a lifelong condition that requires continuous pharmacotherapy to control the associated symptoms and prevent complications.

The DIADEM-I evidence-based approach to weight loss and maintenance was devised from previous observations that early substantial weight loss, use of meal replacement products, and increasing physical activity, supported by frequent patient contact, are associated with optimal weight loss maintenance and cardiometabolic outcomes.[18–20] Weight loss is associated with a reduction in liver and pancreatic fat, resulting in greater hepatic insulin sensitivity and improved pancreatic β-cell function.[8] Additionally, low-energy diets, physical activity, and a combination of the two, improve insulin sensitivity.[21,22] Both the DiRECT[7] and DROPLET[23] clinical trials have shown that substantial weight loss in a primary care setting in the UK is achievable by use of a similar dietary approach to that used in our study. The number of dropouts in our study and the DiRECT study[7] are similar, suggesting that the intervention is acceptable to most participants with diabetes. Furthermore, there was good attendance of the intervention clinics in participants of working age (18–50 years). The reduction in bodyweight observed in participants who received the intensive lifestyle intervention in our study was similar to that of DiRECT,[7] DROPLET,[23] and other previous studies of low-energy diet interventions.[24,25] The weight loss observed in our study, however, was mainly from fat mass, with lean mass being preserved, suggesting potential benefits of incorporating physical activity in the intervention.

There are several key differences between our study, and the DiRECT[7] and DROPLET[23] studies. The dietary intervention in our study was delivered solely by a team of dietitians who were trained in the behavioural aspects of the programme and who were able to give specific tailored dietary advice, particularly during the food reintroduction and maintenance phases. Furthermore, our study emphasised physical activity through personal trainers, with the aim of encouraging the adoption of physical activity for weight loss maintenance. Both the DiRECT[7] and DROPLET[23] studies included mainly white European populations, whereas participants enrolled in our study originated from 13 different countries (nine in the Middle East and four in north Africa). Unlike many previous studies of weight loss interventions, the majority of participants in our study were men (73%), and participants were also about a decade younger than those in the DiRECT[7] and DROPLET[23] studies. In addition, participants enrolled in our study had a significantly shorter duration of disease compared with DiRECT.[7] Of note, the percentage of participants who had been treated by diet alone was much lower in our study (10·2%) than in the DiRECT study (24·2%), suggesting

that there is a greater emphasis on pharmacotherapy in the Middle East and north Africa than in the UK.

Weight loss and lifestyle change have been shown to be associated with significant improvements in glycaemic control and diabetes remission. Studies of bariatric surgery have shown that individuals who attain diabetes remission have significant weight loss, are younger, have shorter disease duration, and are on fewer medications compared with those who do not attain diabetes remission. The main effect of bariatric surgery on diabetes is energy restriction and subsequent weight loss. Bariatric surgery is also associated with a reduction in the number and severity of diabetes complications and mortality from cardiovascular disease.[5,26] Bariatric surgery, however, is not acceptable or available to all patients, and this intervention is unlikely to be the solution for most patients with type 2 diabetes. The Look AHEAD trial[27] used an intensive lifestyle intervention aimed at significant weight loss in individuals with type 2 diabetes. In the post-hoc analysis, the study[27] showed that a 10% weight loss was associated with a 21% reduction in the incidence of cardiovascular outcomes over a follow-up period of 10 years.[28] However, only 11·5% of participants in the intensive lifestyle group had diabetes remission at 1 year compared with 2% of participants in the control group. Participants in the Look AHEAD trial,[27] however, were older (mean age 58·6 years [SD 6·8] in the lifestyle intervention group) and had a median duration of diabetes of 5 years (range 2–10). There was also a strong emphasis on physical activity in the Look AHEAD trial.[27] Compared with the Look AHEAD[27] patient cohort, the DiRECT study[7] used a more intensive dietary intervention in individuals with a shorter duration of diabetes and who were younger, and found that 46% of participants receiving this intervention had diabetes remission accompanied by significant weight loss at 12 months. Our study now extends these previous observations, indicating that an intensive lifestyle intervention, which involves a similar dietary approach to the DiRECT study,[7] but with the addition of a physical activity component, leads to more diabetes remission (61%) in younger participants with a shorter diabetes duration than in the DiRECT study. Furthermore, our study was done in the Middle East and north Africa region, where there is a high prevalence of obesity and diabetes, and we included participants from 13 countries, showing a greater generalisability of this approach.

In our study, both the intervention and control groups had improved glycaemic outcomes, although, in the control group, this was achieved through treating participants with a greater number of diabetes medications than in the intervention group. Glycaemic variability, measured through continuous glucose monitoring, however, improved in the intervention group. Insulin sensitivity was also better in the intervention group compared with the control group. Compared with previous studies, a greater proportion of participants in both groups achieved diabetes remission, with a third of participants in the intervention group having normoglycaemia at 12 months. This difference is likely to be associated with the younger age of participants and the shorter diabetes duration compared with previous studies.

Avoiding diabetes complications extends beyond glycaemic control, and requires blood pressure and lipid control. We found that blood pressure was reduced in both groups, but at the cost of taking antihypertensive medications in the control group. Remarkably, 71·4% of participants in the intervention group had normal blood pressure without medications. Total cholesterol and LDL cholesterol increased in the intervention group, but only 26% of participants were taking lipid-lowering drugs compared with 76% of participants in the control group, and those in diabetes remission no longer wished to take lipid-lowering medications and were no longer in a risk category requiring lipid-lowering medications. Although the lifestyle intervention reduced most risk factors for cardiovascular disease, it is essential to monitor and assess the continuing requirement for lipid-lowering medications when administering such an intervention to patients with type 2 diabetes. Overall, the beneficial effects of the intervention and associated weight loss extended beyond glycaemic control.

More improvements in quality of life were observed in the intervention group compared with the control group, although the difference between the two groups was not significant. Compared with studies that included older individuals (ie, those in the DiRECT study[7]) with a greater number of comorbidities, the quality of life scores in participants in our study were better at baseline (mean EQ-5D scale score was 81·0 [SD 17·2] in our study *vs* 66·4 [19·2] in the DiRECT study[7]), leaving smaller room for improvement by the end of the study. We found that improved glycaemic control in the control group of participants was achieved through use of a greater number of diabetes medications, and it is likely that treatment intensification will, over time, result in a reduction in quality of life. Between baseline and 12 months, the total number of diabetes medications increased from a median of 3 to a median of 5 in the control group, but reduced from a median of 3 to a median of 1 in the intervention group. The self-reported amount of time spent sitting was reduced and walking (MET-min/week) was increased in the intervention group, but there was no difference between groups in terms of increased intensity activity. Notably, resting heart rate between baseline and 12 months was reduced in the intervention group, suggesting that participants had improved aerobic fitness. The team of dietitians consisted of the same group of professionals throughout the study, thus providing greater consistency for participants. However, maintaining a consistent team of personal trainers proved challenging, which made it difficult to support participants in increasing their physical activity. Ongoing qualitative interviews will provide a more detailed assessment of the quality of life of participants during the intervention, and about aspects

related to the intervention, including its effects on physical activity.

There are several strengths to our study. We included a representative sample of young participants with early type 2 diabetes from 13 countries in the Middle East and north Africa region. The high prevalence of obesity and diabetes in young individuals in this region predisposes them to early disease complications and mortality. The proportion of deaths due to diabetes before the age of 60 years in the Middle East and north Africa is 53·3% compared with 31·4% in Europe and 44% in North America.[29] A greater proportion of men were included in our study (72·8%) than were included in the DiRECT study[7] (59·1%), reflecting the higher prevalence of diabetes in men than in women.[30] Further work is required to examine how men and women respond differently to the lifestyle intervention. A greater emphasis on physical activity might have also contributed to the outcomes observed in our study when compared with the DiRECT study.[7] We used nutritionally complete meal replacement products that were already locally available and acceptable to the population.

Our study has several limitations. The intervention was delivered by a single trained multidisciplinary team, which might not be as readily available in other health services. Also, because there was only one team, we could not examine the effect of treatment-by-cluster (ie, variation between different individuals or teams delivering the intervention) in our analysis.[31] Blinding, apart from the final statistical analysis, is difficult in these types of studies. There is always a risk of contamination with individual randomisation in a small geographical area. However, we avoided contamination by ensuring that there was little interaction between the intervention and control groups at study sites. Any contamination, however, would have only diminished the difference observed between the two groups. Another limitation is that we only reported outcomes at 12 months. Nevertheless, the glycaemic control achieved in the intervention group was clinically significant and could contribute to long-term benefits (ie, beyond 12 months) of a reduction in microvascular complications through metabolic memory, even if reversion to diabetes occurs at a later date. If the improved glycaemic control is sustained, it is likely to delay and reduce cardiovascular events, as was observed in the Look AHEAD study.[28,32] Reassuringly, the DiRECT study[7] reported that over a third of the participants remained in remission for 2 years.[11] The reduction in the proportion of participants who had diabetes remission in the DiRECT study[7] was associated with weight regain, suggesting that additional efforts to support weight maintenance after the trial is required. Follow up of the DIADEM-I cohort is ongoing and will inform whether the addition of physical activity to support weight maintenance results in improved long-term outcomes beyond 12 months.

No serious adverse events were associated with the intervention. The adverse events reported in the intervention group were mainly associated with the total diet replacement phase. Constipation and dizziness were the most common adverse events. To avoid any serious adverse events associated with dizziness, antihypertensives were discontinued in most participants in the intervention group. There were no gallbladder-related adverse events. Participants in the intervention group also reported more musculoskeletal problems associated with increasing activity than the control group. The higher prevalence of viral upper respiratory tract infections in the intervention group compared with the control group could have been associated with the frequency of clinic visits; however, it is also possible that weight loss and dietary changes might have had an effect on immune function.

Our study showed that significant weight loss (>15%) was achieved safely by 21% of participants in the lifestyle intervention group. Weight loss was accompanied by diabetes remission in 61% of participants in the intervention group. Importantly, over a third of participants in the intervention group had normoglycaemia at 12 months. Type 2 diabetes occurs insidiously, and by the time it is diagnosed, the affected individual might have had β-cell dysfunction and hyperglycaemia for some time. Instituting lifestyle interventions at the earliest opportunity could capture individuals at a stage when β-cell dysfunction can be reversed and therefore avoid or delay progression to β-cell damage and loss.[8] The results of the DIADEM-I study and other recent studies need to be tested further by incorporating the lifestyle interventions into primary care as a key approach for those with early diabetes. Linking the lifestyle intervention with diabetes screening programmes, will allow individuals identified to have early stage diabetes to be offered a solution to reverse type 2 diabetes at the earliest stage, with potential long-term benefits for health and wellbeing.

Contributors

The principal investigator, ST, conceived the study and designed the intervention. ST, MC, KEN, MTW, and OC contributed to the study design. OC was the clinical trial lead and supported oversight of the study. HZ oversaw the day-to-day conduct of the study with support from SE and SHA. KEN, NEK, RAA, and SHA provided dietetic support. NS provided physician support and oversight. AA-H, AA-N, SA-A, and ABA-S provided logistic support for study implementation. ST, MTW, HZ, and OC contributed to data analysis and drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

Declaration of interests

ST has participated as an advisory board member of Novo Nordisk; is on the board of directors of Droobi Health; and reports a previous educational grant from Cambridge Weight Plan UK for an investigator-initiated clinical research study (ISRCTN21335883). All other authors declare no competing interests.

Data sharing

The corresponding author (ST) is the custodian of the data and will provide deidentified participant data on reasonable request (staheri@me.com), with the completion of a data access agreement.

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