Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial

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Summary

Background The DiRECT trial assessed remission of type 2 diabetes during a primary care-led weight-management programme. At 1 year, 68 (46%) of 149 intervention participants were in remission and 36 (24%) had achieved at least 15 kg weight loss. The aim of this 2-year analysis is to assess the durability of the intervention effect.

Methods DiRECT is an open-label, cluster-randomised, controlled trial done at primary care practices in the UK. Practices were randomly assigned (1:1) via a computer-generated list to provide an integrated structured weight-management programme (intervention) or best-practice care in accordance with guidelines (control), with stratification for study site (Tyneside or Scotland) and practice list size (>5700 or ≤5700 people). Allocation was concealed from the study statisticians; participants, carers, and study research assistants were aware of allocation. We recruited individuals aged 20–65 years, with less than 6 years' duration of type 2 diabetes, BMI 27–45 kg/m², and not receiving insulin between July 25, 2014, and Aug 5, 2016. The intervention consisted of withdrawal of antidiabetes and antihypertensive drugs, total diet replacement (825–853 kcal per day formula diet for 12–20 weeks), stepped food reintroduction (2–8 weeks), and then structured support for weight-loss maintenance. The coprimary outcomes, analysed hierarchically in the intention-to-treat population at 24 months, were weight loss of at least 15 kg, and remission of diabetes, defined as HbA_{1c} less than 6·5% (48 mmol/mol) after withdrawal of antidiabetes drugs at baseline (remission was determined independently at 12 and 24 months). The trial is registered with the ISRCTN registry, number 03267836, and follow-up is ongoing.

Findings The intention-to-treat population consisted of 149 participants per group. At 24 months, 17 (11%) intervention participants and three (2%) control participants had weight loss of at least 15 kg (adjusted odds ratio [aOR] 7·49, 95% CI 2·05 to 27·32; p=0·0023) and 53 (36%) intervention participants and five (3%) control participants had remission of diabetes (aOR 25·82, 8·25 to 80·84; p<0·0001). The adjusted mean difference between the control and intervention groups in change in bodyweight was –5·4 kg (95% CI –6·9 to –4·0; p<0·0001) and in HbA_{1c} was –4·8 mmol/mol (–8·3 to –1·4 [–0·44% (–0·76 to –0·13)]; p=0·0063), despite only 51 (40%) of 129 patients in the intervention group using anti-diabetes medication compared with 120 (84%) of 143 in the control group. In a post-hoc analysis of the whole study population, of those participants who maintained at least 10 kg weight loss (45 of 272 with data), 29 (64%) achieved remission; 36 (24%) of 149 participants in the intervention group maintained at least 10 kg weight loss. Serious adverse events were similar to those reported at 12 months, but were fewer in the intervention group than in the control group in the second year of the study (nine *vs* 22).

Interpretation The DiRECT programme sustained remissions at 24 months for more than a third of people with type 2 diabetes. Sustained remission was linked to the extent of sustained weight loss.

Funding Diabetes UK.

Introduction

Roughly one in 16 adults in the UK and one in ten adults in the USA have type 2 diabetes,[1,2] with a much higher prevalence (up to one in five) apparent in other parts of the world.[3] Diabetes complications are common and expensive to manage, so associated health-care costs are enormous despite the improvements offered through application of clinical guidelines. Type 2 diabetes is particularly devastating for the growing numbers of younger people affected, who tend to be more obese and lose more life years through disabling and painful complications.[4]

The extreme strength of association between excess weight gain in adult life and type 2 diabetes makes a causal association highly likely. The specific importance of intra-abdominal fat and large waist circumference has been long recognised, and the twin-cycle mechanism, driven by a damaging but reversible accumulation of

Lancet Diabetes Endocrinol 2019

Published Online
March 6, 2019
http://dx.doi.org/10.1016/S2213-8587(19)30068-3

See Online/Comment
http://dx.doi.org/10.1016/S2213-8587(19)30071-3

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Research in context

Evidence before this study

Before undertaking the Diabetes Remission Clinical Trial (DiRECT) study, we searched PubMed for evidence on remissions of type 2 diabetes with all potential interventions. For the present analysis, we reviewed new literature on remission of type 2 diabetes through weight management, searching PubMed for articles published in English since the publication of the 12-month results of DiRECT (December, 2017) up to Dec 31, 2018, using search terms "clinical trial", "remission", "type 2 diabetes", and "weight loss". The search identified eight reports, of which only three covered weight-loss interventions; of these, two were reports from DiRECT and one reported results of laparoscopic surgery, which was deemed not relevant.

Added value of this study

The present study extends to 2 years evidence for durable remission of type 2 diabetes following diet-induced weight loss. The results also provide evidence of wider benefits relating to blood pressure, blood lipids, and wellbeing.

Implications of all the available evidence

The findings from DiRECT will provide added impetus to extend the early measures already announced to change existing National Health Service policy and practice for the routine management of type 2 diabetes. These data, and other relevant data on diabetes control, HbA_{1c}, and weight management, all point towards the likelihood that intensive weight management has the potential to reduce or delay complications of type 2 diabetes and improve clinical outcomes.

ectopic fat within the liver and pancreas in susceptible individuals, has been consistently observed.[5–7] Results from several studies have shown that weight loss of at least 10–15 kg frequently leads to normalisation of blood glucose concentrations in people with short-duration type 2 diabetes.[8–11] In the Diabetes Remission Clinical Trial (DiRECT), we reported that almost half (68 [46%] of 149) of a group with type 2 diabetes of up to 6 years' duration achieved remission at 1 year by following a structured weight-management programme;[12] among the 36 participants in the intervention group who achieved target weight loss of 15 kg or more, 31 (86%) had achieved remission at 1 year. These results have changed perceptions of a condition previously assumed to be permanent and demanding lifelong drug treatment.

Sufficient weight loss for remission (>10 kg) can be achieved in various ways, including bariatric surgery, but also through use of a low-calorie formula for total diet replacement, as assessed in DiRECT. The major questions are whether remission can be durable, whether it can be successfully delivered at scale in primary care (where most patients with type 2 diabetes are usually managed), and by how much vascular complications of diabetes can be delayed or avoided. One key issue is how best to support long-term maintenance of weight loss and remission of type 2 diabetes. Maintenance of weight loss is the greatest challenge faced by individuals and is an under-researched area with little robust evidence; notably, in the past, weight loss based on use of formula diets was commonly regarded as effective only in the very short term.[13]

DiRECT was designed to test an integrated weight-management programme delivered in primary care, with an initial period of effective weight loss (including use of low-calorie formula-based total diet replacement), stepped food reintroduction with emphasis on energy balance, and then structured support for weight loss maintenance with provision for relapse management. Here we report the clinical outcomes in the intervention and control groups at 2 years, in order to assess the durability of the intervention effect identified at the 1-year timepoint.[12]

Methods

Study design and participants

DiRECT was a 2-year, open-label, cluster-randomised controlled trial done at 49 primary care (general practitioner [GP]) practices in Scotland and the Tyneside region of England, UK. The protocol, including details of recruitment methods, study conduct, and planned analyses, has been published elsewhere,[14] as have the baseline characteristics[15] and the primary study findings at 1 year.[12]

No specific eligibility criteria for GP practices were defined. Eligible participants were aged 20–65 years, had been diagnosed with type 2 diabetes within the previous 6 years, and had a BMI of 27–45 kg/m². Exclusion criterial included current insulin use, HbA_{1c} of 12% (108 mmol/mol) or higher, weight loss of more than 5 kg within the previous 6 months, and a recent recorded estimated glomerular rate of less than 30 mL/min per 1·732 m². Other exclusion criteria were severe or unstable heart failure, participation in any other trial, substance misuse, known cancer, myocardial infarction within the previous 6 months, learning difficulties, current treatment with anti-obesity drugs, eating disorders or purging behaviours at any time, pregnancy or consideration of pregnancy, hospital admission for depression at any time, and current use of antipsychotic drugs.

As reported previously,[12] the criteria for diagnosis of type 2 diabetes were tightened in an approved protocol amendment, shortly after recruitment began, to exclude patients who had already achieved a non-diabetic HbA_{1c} level. As revised, the inclusion criterion specified that a prospective participant's most recent HbA_{1c} value should be greater than 6·0% (42 mmol/mol) and, if less than

6·5% (48 mmol/mol), they should still be receiving antidiabetes drug treatment.

Ethics approval for the trial was granted by West 3 Ethics Committee in January, 2014, with additional approvals by the National Health Service (NHS) health boards in Scotland and clinical commissioning groups in Tyneside. All participants provided written informed consent.

Randomisation and masking

GP practices that agreed to participate were randomly assigned (1:1) by the Robertson Centre for Biostatistics (University of Glasgow, Glasgow, UK), independently of the clinical research team and via a computer-generated list, to provide either an evidence-based weight management programme (Counterweight-Plus; intervention) or best-practice care in accordance with guidelines (control). Randomisation was stratified by practice list size (>5700 or <5700 people) and study region (Scotland or Tyneside).

The study statisticians (AM and C-MM) were masked to treatment allocation for the analysis. Because of the nature of the intervention, participants, carers, and research assistants who collected outcome data were aware of group allocation.

Procedures

The intervention programme (Counterweight-Plus), delivered entirely within a routine primary care setting by a trained NHS dietitian or nurse (as available locally), consisted of total diet replacement (825–853 kcal per day formula diet) for 3–5 months (flexible duration to allow for individual goals and circumstances), stepped food reintroduction (6–8 weeks), and then structured support for weight-loss maintenance.[12] For the maintenance phase, from the end of food reintroduction up to 24 months, participants were offered monthly 30 min appointments with the dietitian or practice nurse, using tailored workbooks. In the event of weight regain greater than 2 kg during the maintenance phase, participants were offered a rescue plan of 2–4 weeks' partial meal replacement; if weight regain was greater than 4 kg, participants were offered total diet replacement (4 weeks) and food reintroduction (4 weeks), with the option of orlistat treatment. Advice to increase daily physical activity was reinforced at each visit during the maintenance phase, although no specific targets were set. Both antidiabetes and antihypertensive drugs were withdrawn for the intervention participants on day 1 of total diet replacement, with protocols for their reintroduction if necessary, according to clinical guidelines.[14] Antihypertensive drugs were withdrawn to avoid postural hypotension, since blood pressure generally decreases on commencement of a low-energy diet.[7]

The control participants continued with best-practice routine care with no change to dietary, medication, or exercise advice because of enrolment in the trial. They were reviewed by the study team to collect study outcome data at baseline, 12 months, and 24 months. Apart from the initial phase of the intervention, participants in both groups continued to receive diabetes care under current guidelines and standards from the National Institute of Health and Care Excellence in England[16] and the Scottish Intercollegiate Guidelines Network in Scotland.[17] These guidelines do not at present include any recommendations for therapeutic trials of drug withdrawal, which are left to the discretion of doctors in the event of clinical improvement through lifestyle changes. All study appointments took place at the participants' own GP practices.

Outcomes

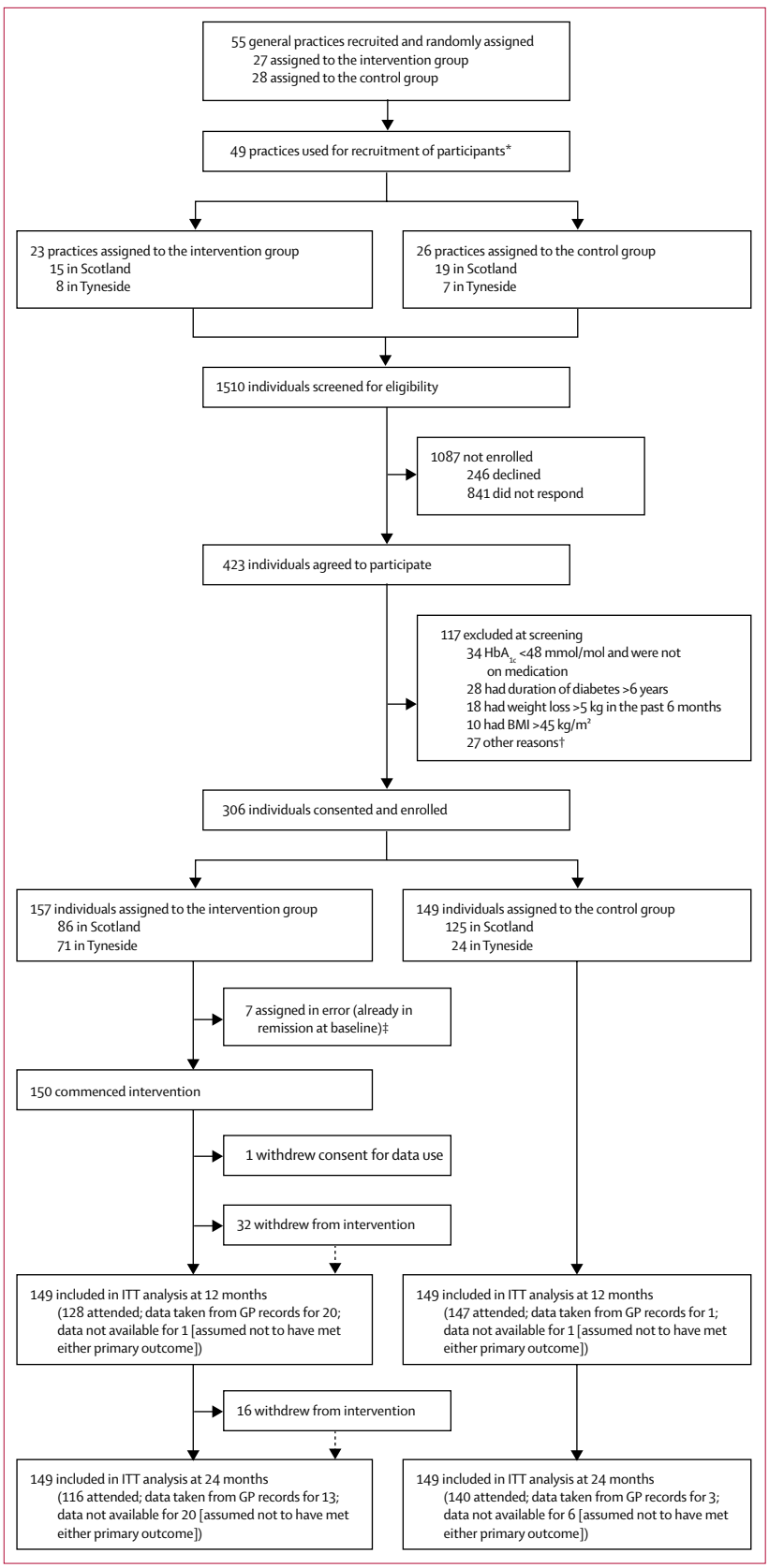
The coprimary outcomes assessed at 24 months were a reduction in bodyweight of 15 kg or more, and remission of diabetes, defined as HbA_{1c} less than 6·5% (<48 mmol/mol) after withdrawal of antidiabetes drugs at baseline (independent of status at 12 months).[18,19] We also report data for absolute changes in bodyweight and HbA_{1c}, as well as the number of antidiabetes and antihypertensive drugs and the number of participants on any antidiabetes drugs at baseline, 12 months, and 24 months (post hoc). Secondary outcomes were quality of life, as measured by visual analogue scale, and general wellbeing by Health Utility Score, both from the three-level EuroQol 5 Dimensions (EQ-5D-3L); serum lipids (triglycerides, HDL cholesterol, and total cholesterol); and physical activity. Other prespecified outcomes were sleep quality, systolic blood pressure, and serious adverse events collected from GP records, as detailed in the trial protocol.[14] Outcome data were collected at baseline and repeated at 12 and 24 months as planned. All prespecified outcomes are reported here apart from physical activity and sleep quality data, which have not yet been analysed.

We additionally assessed changes in medication and remission in the overall study population following weight loss of less than 5 kg, 5 kg to less than 10 kg, 10 kg to less than 15 kg, and 15 kg or more, as well as weight loss of at least 10 kg, as post-hoc analyses. Finally, we also assessed the change in weight by achieved remission at each timepoint and the baseline characteristics of those attending the 24-month visit compared with those who did not.

For participants who ceased to engage and did not attend their 12-month or 24-month trial appointments, data from GP records (within a window of 100 days before or after the scheduled follow-up date) were used, if available, as specified in the study protocol.[15]

Statistical analysis

The planned analyses were done at the individual level, in accordance with the intention-to-treat principle. The coprimary outcomes were analysed hierarchically, with the weight-loss outcome first, with no adjustment of the p values for multiple comparisons. For participants who did not attend the 12-month or 24-month study assessments, and for whom data could not be obtained from GP records,



we assumed that the coprimary outcomes were not met. For the main analysis of secondary outcomes, no assumptions were made regarding missing data.

In the sample size calculation for the trial, we determined that recruitment of 280 participants would be required to achieve 80% power. These calculations assumed diabetes remission in 22% of participants in the intervention group at 1 year (the effect size deemed potentially important, a priori) compared with an estimated 5% in the control group, enrolment of ten participants per practice (fixed), an intraclass correlation coefficient of 0·05 to account for cluster randomisation, and an estimated dropout rate of 25% within 12 months. No data were available to inform a separate sample size calculation for the 24-month analyses.

Outcomes were compared between groups by use of mixed-effects regression models, with adjustment for GP practice as a random effect. Logistic models were used for binary outcomes and Gaussian models were used for continuous outcomes. If possible, models were adjusted for the minimisation variables (study centre and practice list size), age, sex, duration of diabetes, and HbA_{1c} at baseline. Models of continuous outcomes were also adjusted for the baseline measurement of the outcome. If models failed to converge, models with fewer adjustment variables were attempted. For serum triglycerides, groups were compared with a linear regression model of log-transformed values, with adjustment for baseline log triglycerides.

For continuous outcomes, model fit was assessed visually with normal probability plots. When substantial departure from a normal distribution was identified, groups were also compared with non-parametric Wilcoxon–Mann–Whitney tests, using both the 24-month outcome value and the change from baseline. For binary outcomes, when the number of cases or non-cases was zero in one of the randomised groups and the regression model would not converge, we compared groups with Fisher's exact test.

Statistical analyses were done with R for Windows, version 3.2.4.

The DiRECT trial is registered with the ISRCTN registry, number 03267836.

Figure 1: **Trial profile**
ITT=intention-to-treat. GP=general practitioner. *Four intervention practices and two control practices were not required for recruitment, which was done sequentially by practice to allow for training of practice staff; therefore, 49 practices were asked to recruit participants. †Other reasons for exclusion were BMI <27 kg/m² (n=3), age >65 years (n=3), substance misuse (n=3), unable to attend appointments (n=2), unable to comply with diet (n=2), poor English (n=2), on antipsychotic medication (n=2), heart failure (n=1), other medical condition (n=1), hospital admission for depression (n=1), participation in another clinical trial (n=1), recent cardiac event (n=1), recent pancreatitis (n=1), advanced renal disease (n=1), did not attend baseline appointment (n=1), receiving insulin (n=1), and could not attend baseline before close of recruitment (n=1). ‡Baseline HbA_{1c} <6·5% (48 mmol/mol).

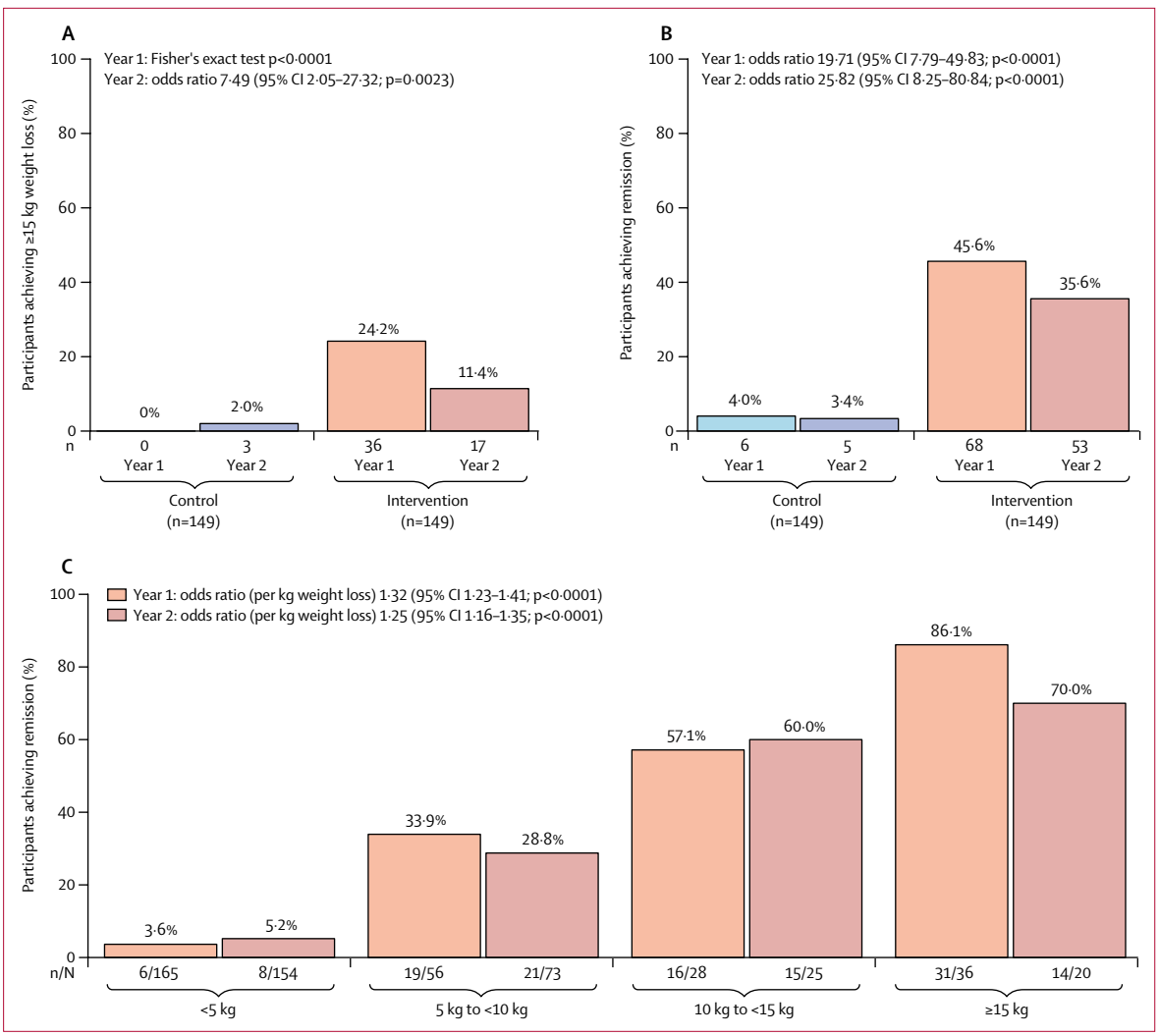


Figure 2: **Primary outcomes and remission of type 2 diabetes in relation to weight loss at 12 and at 24 months**
Regression models adjusted for practice list size, study centre, and a random effect for practice. (A) First coprimary outcome, achievement of at least 15 kg weight loss, by randomised group. (B) Second coprimary outcome, remission of type 2 diabetes (HbA_{1c} <48 mmol/mol [6·5%] and off antidiabetes drugs since baseline), by randomised group. (C) Remission of type 2 diabetes in relation to weight loss achieved (both randomised groups combined).

Role of the funding source

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

Results

Between July 25, 2014, and Aug 5, 2016, we recruited 306 individuals from 49 practices (23 intervention and 26 control); the intention-to-treat population consisted of 149 participants in each group (figure 1). As reported previously,[12,15] baseline characteristics were similar between groups (appendix).

116 (78%) of 149 participants in the intervention and 140 (94%) of 149 in the control group attended the 24-month study assessment, thus overall 42 (14%) of 298 randomised participants did not attend at 24 months. Selected baseline characteristics of those who attended this visit compared with those who did not are shown in the appendix. Additional data for bodyweight and HbA_{1c} were obtained from GP records, where available, such that data at 24 months for bodyweight and for HbA_{1c} were available for 272 (91%) participants (129 [87%] in the intervention group and 143 [96%] in the control group). For the intention-to-treat analysis, the remaining 26 participants with no data at 24 months, who did not attend the 24-month study assessment, and for whom GP records were not available because they had moved residence or practice and could not be traced, were assumed not to have met either primary outcome (figure 1).

The intervention group participants attended an average of 7·7 appointments of the possible 12 visits at monthly intervals during the second year (between

See Online for appendix

	Baseline	12 months	24 months	Change from baseline at 24 months	Intervention effect at 24 months (95% CI)	ICC
Bodyweight (kg)	..	..	..	..	−5·43 (−6·87 to −3·99; p<0·0001)	<0·01
Intervention (n=129*)	101·0 (16·7)	90·4 (16·4)	93·2 (17·2)	−7·6 (6·5)	..	..
Control (n=143*)	98·8 (16·1)	97·7(16·4)	96·4 (16·3)	−2·3 (5·2)	..	..
HbA_{1c} (mmol/mol)	..	..	..	..	−4·82 (−8·28 to −1·36; p=0·0063)	<0·01
Intervention (n=129*)	60·4 (13·7)	50·6(13·3)	54·4 (15·9)	−5·2 (16·4)	..	..
Control (n=143*)	58·2 (11·5)	59·6(12·1)	58·6 (14·4)	0·4 (15·5)	..	..
HbA_{1c} (%)	..	..	..	..	−0·44 (−0·76 to −0·13; p=0·0063)	<0·01
Intervention (n=129*)	7·7 (1·3)	6·8(1·2)	7·1 (1·5)	−0·5 (1·5)	..	..
Control (n=143*)	7·5 (1·1)	7·6(1·1)	7·5 (1·3)	0·0 (1·4)	..	..
Number of prescribed oral antidiabetes drugs†	..	..	..	..	−0·86 (−1·02 to −0·69; p<0·0001)	<0·01
Intervention (n=129*)	1·1 (0·9)	0·4(0·7)	0·6 (0·9)	−0·6 (0·8)	..	..
Control (n=143*)	1·1 (0·8)	1·3(0·9)	1·3 (1·0)	0·3 (0·6)	..	..
Number of prescribed antihypertensive drugs	..	..	..	..	−0·36 (−0·53 to −0·19; p<0·0001)	0·03
Intervention (n=129*)	1·0 (1·2)	0·5(0·7)	0·7 (0·9)	−0·3 (0·9)	..	..
Control (n=143*)	1·0 (1·1)	1·0 (1·0)	1·1 (1·1)	0·1 (0·5)	..	..
Systolic blood pressure (mm Hg)	..	..	..	..	−3·43 (−6·70 to −0·16; p=0·040)	0·01
Intervention (n=113*)	132·7 (17·5)	133·0 (16·3)	130·3 (13·6)	−4·3 (18·7)	..	..
Control (n=140*)	137·2 (16·0)	135·8 (14·6)	135·4 (14·0)	−1·4 (13·4)	..	..
EQ-5D Health Utility Score	..	..	..	..	0·024 (−0·021 to 0·070; p=0·29)	<0·01
Intervention (n=113*)	0·798 (0·288)	0·793 (0·278)	0·819 (0·268)	−0·002 (0·205)	..	..
Control (n=140*)	0·802 (0·281)	0·759 (0·302)	0·788 (0·253)	−0·013 (0·194)	..	..
Quality of life (EQ-5D VAS)	..	..	..	..	4·64 (0·39 to 8·89; p=0·032)	0·04
Intervention (n=113*)	65·8 (19·1)	73·7 (19·0)	75·2 (17·3)	8·2 (20·1)	..	..
Control (n=140*)	72·1 (19·6)	69·1 (15·6)	74·0 (16·8)	1·7 (15·1)	..	..
Triglycerides (mmol/L)‡	..	..	..	..	−0·14 (−0·23 to −0·04; p=0·0055)	<0·01
Intervention (n=105*)	2·1 (1·4)	1·7 (1·4)	1·6 (1·0)	−0·4 (1·2)	..	..
Control (n=138*)	1·9 (0·9)	2·0 (1·2)	1·7 (0·9)	−0·2 (0·7)	..	..
HDL cholesterol (mmol/L)	..	..	..	..	0·09 (0·02 to 0·16; p=0·013)	0·03
Intervention (n=105*)	1·1 (0·3)	1·2 (0·3)	1·3 (0·4)	0·2 (0·3)	..	..
Control (n=138*)	1·2 (0·3)	1·2 (0·3)	1·3 (0·4)	0·1 (0·2)	..	..
Total cholesterol (mmol/L)	..	..	..	..	0·30 (0·01 to 0·60; p=0·045)	0·06
Intervention (n=105*)	4·3 (1·2)	4·5 (1·3)	4·7 (1·2)	0·4 (1·3)	..	..
Control (n=138*)	4·3 (1·2)	4·3 (1·1)	4·4 (1·2)	0·1 (0·9)	..	..
Number of participants on any antidiabetes drugs (binary outcome)§	..	..	..	..	0·03 (0·01 to 0·08; p<0·0001)§	NA
Intervention (n=129*)	111/149 (74%)	39/148 (26%)	51/129 (40%)	..	..	..
Control (n=143*)	115/149 (77%)	121/148 (82%)	120/143 (84%)	..	..	..

Data are mean (SD), unless otherwise specified; intervention effects reported as estimated mean differences (intervention minus control), based on mixed-effects linear regression model, adjusted for randomised group, baseline value, age, sex, duration of diabetes and HbA_{1c} at baseline, study centre (Tyneside or Scotland), and practice list size (≤5700, >5700) as fixed effects, and general practitioner practice as a random effect. ICC=intraclass correlation coefficient. EQ-5D=EuroQol 5 Dimensions. VAS=visual analogue scale. NA=not applicable.*n is the number of participants with data at 24-month follow-up (total n=149 at baseline for both intervention and control groups). †Number (%) of participants prescribed 0, 1, or ≥2 oral antidiabetes drugs, respectively, were 38/149 (26%), 65/149 (44%), and 46/149 (31%) in the intervention group at baseline; 34/149 (23%), 79/149 (53%), and 36/149 (24%) in the control group at baseline; 109/148 (74%), 26/148 (18%), and 13/148 (9%) in the intervention group at 12 months; 27/148 (18%), 69/148 (47%), and 52/148 (35%) in the control group at 12 months; 78/129 (60%), 29/129 (22%), and 22/129 (17%) in the intervention group at 24 months; and 23/143 (16%), 70/143 (49%), and 50/143 (35%) in the control group at 24 months. ‡Log-transformed values were used in the regression analysis. §For this binary outcome, data are n/N (%) and intervention effect is reported as odds ratio (95% CI).

Table 1: **Outcomes at 24 months**

12 and 24 months); those who attended the 2-year follow-up visit attended 9·6 out of the maximum of 12 visits.

At 24 months, weight loss of 15 kg or more from baseline was recorded in 17 (11%) of 149 participants in the intervention group and by three (2%) of 149 participants in the control group (adjusted odds ratio [aOR] 7·49, 95% CI 2·05–27·32, p=0·0023; figure 2A). In the intervention group, 36 (24%) of 149 participants

maintained at least 10 kg weight loss at 24 months (post-hoc analysis). Absolute mean bodyweight by study group at each timepoint is shown in table 1.

At 24 months, diabetes was in remission in 53 (36%) of 149 participants in the intervention group and five (3%) of 149 participants in the control group (aOR 25·82, 95% CI 8·25–80·84; p<0·0001; figure 2B).

For the entire study population for whom 24-month data were available (n=272), remission at 24 months was achieved by eight (5%) of 154 participants who lost less than 5 kg, 21 (29%) of 73 participants who maintained 5 kg to less than 10 kg weight loss, 15 (60%) of 25 participants who maintained 10 kg to less than 15 kg weight loss, 29 (64%) of 45 participants who maintained at least 10 kg weight loss, and 14 (70%) of 20 participants who lost 15 kg or more (post-hoc analysis; figure 2C). Four participants (out of 50 with weight gain [8%]) were in remission at both 12 months and 24 months despite small weight gains (0·4–1·3 kg) at 24 months. These individuals all had baseline HbA_{1c} between 6·5% (48 mmol/mol) and 6·63% (49 mmol/mol). Of participants on antidiabetes drugs at 24 months, 22 (18%) of 119 participants in the control group and none of 51 in the intervention group had an HbA_{1c} below 48 mmol/mol (6·5%) at 24 months. In the control group, four (3%) of 119 had HbA_{1c} below 42 mmol/mol (6·0%) at 24 months. The only intervention participant who received a drug treatment after baseline withdrawal developed gestational diabetes and required insulin only during pregnancy. At 24 months, of the 129 participants in the intervention group with data on medication, 53 (41%) were in remission, 51 (40%) were on antidiabetes drugs, and 25 (19%) had not achieved remission but had not been commenced on drug treatment. Post-hoc analyses were done on the change in weight by achieved remission at each timepoint and the baseline characteristics of those attending the 24-month visit compared with those who did not. The results of these analyses show that remission status at each stage aligns closely to degree of weight loss, and that participants who did not attend the 24-month visit were younger and had somewhat more adverse risk factors at baseline than those who did attend (appendix).

Between baseline and 24 months, mean bodyweight fell by 7·6 kg (SD 6·5) in the intervention group and by 2·3 kg (5·2) in the control group (adjusted difference in weight change between groups at 24 months –5·43 kg, 95% CI –6·87 to –3·99; p<0·0001; table 1).

Between 12 and 24 months, mean bodyweight increased by 2·6 kg (SD 5·0) in the intervention group and decreased by 1·3 kg (4·2) in the control group (adjusted difference in weight change between groups 3·34 kg, 95% CI 2·18–4·50; p<0·0001). In the intervention group, participants who maintained remission between 12 and 24 months (n=48), after having lost a mean of 15·5 kg (6·6) during year 1, regained a mean of 4·3 kg (3·7). In those who relapsed after 12 months (n=15), weight regain was greater (7·1 kg [5·4]; *t* test p=0·073) than in those who maintained remission, after having lost a mean of 12·0 kg (7·7). The group not in remission at 12 months (n=62 with weight data at both 12 and 24 months) had a mean weight gain of 0·26 kg (SD 4·7) after having lost 5·8 (6·4) at 12 months. Over the 24 months from baseline, those who maintained remission (n=53) lost a mean of 10·4 kg (SD 6·8) bodyweight, those who were in remission at 12 months but relapsed at 24 months (n=17) lost 3·7 kg (SD 5·9), and those who did not achieve remission at 12 or 24 months (n=197) lost 3·2 kg (5·2; appendix). Figure 3 shows the results of a post-hoc analysis of weight during the trial for intervention participants who continued to attend appointments (in whom the initial weight loss was largely sustained), those who stopped attending at each stage (where variable weight regain was evident), and for control participants.

Of 143 intervention group participants with data from during treatment phases available, about half required relapse management with brief partial diet replacement or total diet replacement with the offer of orlistat treatment during the 2 years: 71 (50%) did not have any rescue plan, 49 (34%) had one, 15 (10%) had two, and eight (6%) had three or more rescue plan phases. Of the participants in the intervention group, none of 148 with data available were receiving orlistat at 12 months and three (2%) of 129 with data available were receiving orlistat at 24 months.

In the control group, mean HbA_{1c} remained similar between baseline (58·2 mmol/mol [SD 11·5]; 7·5% [1·1])

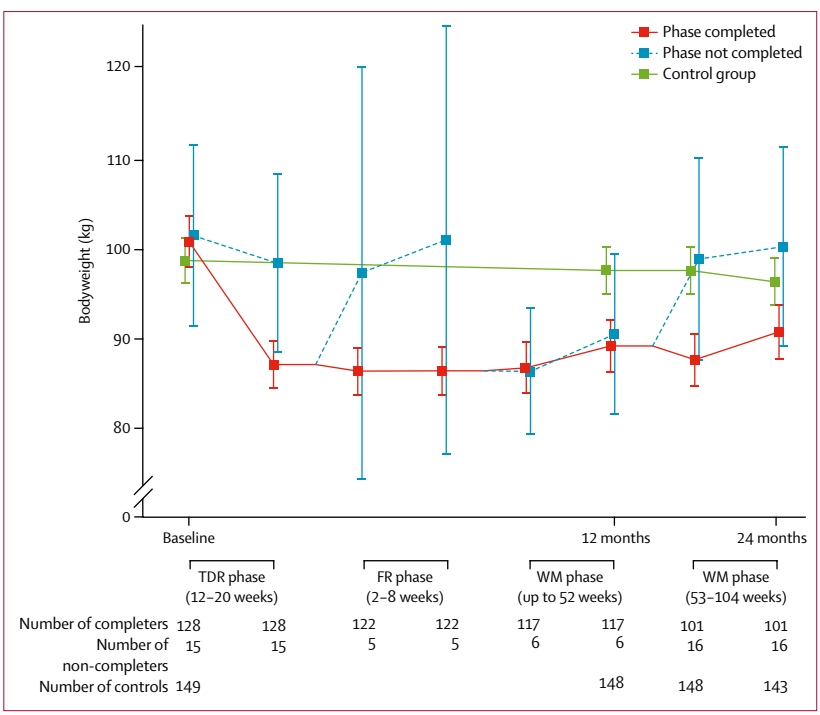


Figure 3: **Changes in bodyweight of participants who remained in the trial and those who withdrew during each phase of the intervention**

Error bars represent 95% CIs. The number shown as withdrawn from treatment decreases during the food reintroduction (FR) stage because of one participant opting to move straight from total diet replacement (TDR) to weight maintenance (WM).

	Control (n=149)	Intervention (n=157)
Number of serious adverse events	25	15
Number of participants with any serious adverse event	19 (13%)	11 (7%)
Cardiac disorders	1 (1%)	3 (2%)
Acute myocardial infarction	0	1 (1%)
Angina pectoris	0	1 (1%)
Atrial fibrillation	1 (1%)	0
Coronary artery disease	0	1 (1%)
Gastrointestinal disorders	1 (1%)	3 (2%)
Abdominal pain	0	1 (1%)
Abdominal strangulated hernia	0	1 (1%)
Diverticulum	0	1 (1%)
Gastric disorder	1 (1%)	0
General disorders and administration-site conditions	1 (1%)	0
Sudden death	1 (1%)	0
Hepatobiliary disorders	1 (1%)	1 (1%)
Cholelithiasis	0	1 (1%)
Non-alcoholic steatohepatitis	1 (1%)	0
Infections and infestations	3 (2%)	2 (1%)
Bacterial arthritis	1 (1%)	0
Diverticulitis	1 (1%)	1 (1%)
Urinary tract infection	0	1 (1%)
Wound infection	1 (1%)	0
Injury, poisoning, and procedural complications	1 (1%)	2 (1%)
Humerus fracture	1 (1%)	0
Incisional hernia	0	1 (1%)
Synovial rupture	0	1 (1%)
Musculoskeletal and connective tissue disorders	1 (1%)	0
Back pain	1 (1%)	0
Neoplasms*	5 (3%)	0
Bladder cancer	1 (1%)	0
Colon cancer	2 (1%)	0
Prostate cancer	1 (1%)	0
Renal cell carcinoma	1 (1%)	0
Nervous system disorders	4 (3%)	2 (1%)
Cerebellar infarction	1 (1%)	0
Cerebrovascular accident	1 (1%)	0
Dizziness	0	1 (1%)
Guillain–Barré syndrome	1 (1%)	0
Presyncope	0	1 (1%)
Sciatica	0	1 (1%)
Seventh nerve paralysis	1 (1%)	0
Pregnancy, puerperium, and perinatal conditions	0	1 (1%)
HELLP syndrome	0	1 (1%)
(Continued from previous column)		
Respiratory, thoracic, and mediastinal disorders	4 (3%)	0
Asthma	2 (1%)	0
Dyspnoea	2 (1%)	0
Surgical and medical procedures	1 (1%)	0
Toe amputation	1 (1%)	0
Vascular disorders	1 (1%)	0
Aortic aneurysm rupture	1 (1%)	0

Data are number of participants (%), unless otherwise specified. Serious adverse events are classified by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term; participants could have more than one type of event, so numbers of participants with given events do not necessarily add up to the total with any events within an organ class or with any serious adverse event. HELLP=haemolysis, elevated liver enzymes, and low platelet count. *Benign, malignant, and unspecified; including cysts and polyps.

Table 2: **Serious adverse events from baseline to 24 months**

and 24 months (58·6 mmol/mol [14·4]; 7·5% [1·3]), with 115 (77%) of 149 participants receiving antidiabetes drugs at baseline, increasing to 120 (84%) of 143 participants at 24 months. In the intervention group, mean HbA_{1c} fell between baseline (60·4 mmol/mol [13·7]; 7·7% [1·3]) and 24 months (54·4 mmol/mol [15·9]; 7·1% [1·5]; adjusted mean difference –4·82 mmol/mol [95% CI –8·28 to –1·36; p=0·0063]), with 111 (74%) of 149 participants receiving antidiabetes drugs at baseline and 51 (40%) of 129 participants doing so at 24 months.

Of those on antidiabetes drugs at 24 months, 22 (18%) of 119 participants in the control group with available data and none of 51 participants in the intervention group had HbA_{1c} below 48 mmol/mol (6·5%) at 24 months; and four (3%) of 119 in the control group had HbA_{1c} below 42 mmol/mol (6·0%) at 24 months.

Mean systolic blood pressure at 24 months had decreased by 1·4 mm Hg (SD 13·4) from baseline in the control group and by 4·3 mm Hg (18·7) in the intervention group (adjusted mean difference –3·43 mm Hg, 95% CI –6·70 to –0·16; p=0·040), with 86 (60%) of 143 participants in the control group and 61 (47%) of 129 participants in the intervention group receiving antihypertensive drugs at 24 months (aOR 0·31, 95% CI 0·14 to 0·71; p=0·0058).

Serum triglyceride concentration at 24 months decreased below baseline values by a mean of 0·2 mmol/L (SD 0·7) in the control group and by a mean of 0·4 mmol/L (1·2) in the intervention group (adjusted mean difference in log-transformed values –0·14, 95% CI –0·23 to –0·04; p=0·0055; table 1). At 24 months compared with baseline, HDL cholesterol had increased by a mean of 0·1 mmol/L (SD 0·2) in the control group and by a mean of 0·2 mmol/L (0·3) in the intervention group (adjusted mean difference 0·09, 95% CI 0·02 to 0·16; p=0·013). Total cholesterol had increased by a mean of 0·1 mmol/L (0·9) in the control group and by a mean of 0·4 mmol/L (1·3) in the intervention group (adjusted mean difference 0·30, 0·01 to 0·60; p=0·045; table 1).

The total numbers of serious adverse events reported for the 24 months of DiRECT were 15 (in 11 participants) in the intervention group and 25 (in 19 participants) in the control group (table 2). Although there had been no substantial difference at 12 months,[12] in the second year of DiRECT, six participants in the intervention group had a total of nine serious adverse events and 16 participants in the control group had a total of 22 serious adverse events (binomial test based on number of events p=0·029; Fisher's exact test based on number of participants with events p=0·026). None of these events led to withdrawal from the study. The serious adverse events included several vascular events in the control group (two cerebrovascular accidents, one toe amputation, one aortic aneurysm rupture, and one sudden death), compared with one non-fatal myocardial infarction in the intervention group in a participant who had not attended for review at either 12 months or 24 months. Two other serious adverse events in the intervention group, both in one participant during the first year of the trial (cholelithiasis and abdominal pain), were deemed to be potentially related to the intervention. The one sudden death in the control group was the only death that occurred during the study.

Quality of life assessed by visual analogue scale at 24 months improved more in the intervention group (median change from baseline 10·0, IQR 0·0 to 20·0) than in the control group (2·5, –5·0 to 9·0); mean values are shown in table 1 (adjusted mean difference 4·64, 95% CI 0·39 to 8·89; p=0·032). General wellbeing as assessed by the Health Utility Score did not change significantly (table 1).

Post-hoc analysis showed that in the whole study population, likelihood of remission at 24 months (n=58/298 [19%]) was higher for men (aOR for women *vs* men 0·44, 95% CI 0·22–0·88; p=0·020) and increased with age (aOR per year 1·08, 1·03–1·13; p=0·0020), weight loss from baseline (aOR per kg lost 1·20, 1·11–1·29; p<0·0001), and weight change from 12 to 24 months (aOR per kg gained 1·11, 1·03–1·21; p=0·010). Likelihood of remission at 24 months was not affected by baseline BMI (aOR per kg/m² 0·99, 0·92–1·06; p=0·77) or duration of diabetes within the 6-year range included in the study (aOR per year 0·92, 0·76–1·11; p=0·39). Where it could be assessed, the effects of sex, weight change, and duration of diabetes on rates of remission did not differ significantly between the intervention and control groups (p for interaction: sex p=0·31; weight change from 12 to 24 months p=0·47; duration of diabetes within the 6-year range studied p=0·11). All models were adjusted for treatment, practice list size, centre, and a random effect for practice.

Discussion

The 2-year results of DiRECT show that continuing remission of type 2 diabetes is possible. Type 2 diabetes was reversible to a non-diabetic state over 24 months for 36% (53/149) of the group that received the primary care-based weight-management intervention, down from the 46% (68/149) who had achieved remission at 12 months.[12] Notably, 70% (14/20) of those who maintained a weight loss of more than 15 kg remained in remission at 24 months. These data extend the first-year results of DiRECT by showing that achieving and maintaining weight loss is the dominant factor behind remission of type 2 diabetes. Participants who reverted to diabetes between 12 and 24 months regained more weight than those who maintained remission. The coprimary outcome of at least 15 kg weight loss was maintained by 11% (17/149) at 24 months, down from 24% (36/149) at 12 months.[12] Blood pressure, lipids, and quality of life improved with the intervention. There were fewer serious adverse events in the intervention group in the second year. The overall diabetes-related cardiometabolic risk profile improved, with reduced lipids and fewer participants requiring antihypertensive drugs to control blood pressure than in the control group.

To our knowledge, DiRECT is the first study designed to test whether, and for how long, dietary weight loss can generate remission of type 2 diabetes. The programme used differs from many weight-management treatments in its structured design, with a three-phase integrated structure, focusing from the outset on the need for long-term maintenance of weight loss. The importance of a formalised rescue plan is emphasised by the observation that almost half of the intervention group required this additional intervention. Of the intervention group participants for whom medication data were available who were not in remission at 24 months (76 of 129), 51 were on antidiabetes drugs and 25 were not. Weight regain was less than in many published studies[13] but remains a challenge. The observed weight regain and remission rates compare favourably with those in the Look AHEAD study,[20] which delivered an intensively supported programme in specialist US diabetes centres, combining substantial increases in physical activity and dietary programmes. Notably, losing more than 10 kg bodyweight in Look AHEAD was associated with reduced cardiovascular events in a post-hoc analysis.[21] Remission of type 2 diabetes was not the primary outcome in Look AHEAD, but was reported in 218 (10%) of 2090 intervention participants at 2 years, with average weight loss slightly below 6 kg.[22] The DiRECT intervention has similarities with Look AHEAD, but was designed specifically for achieving remission of type 2 diabetes, with a view to delivery at scale for the very large numbers of people with the disease in a routine primary care setting. The results will help to overcome reluctance to offer weight management in primary care, whether through unfamiliarity with practical weight management or a belief that weight regain is inevitable and usually complete. Weight changes at 24 months in DiRECT are similar to those reported from the same programme in a prospective audit of its routine use in other primary care and community settings, which showed similar results for

people with and without type 2 diabetes.[23] The resources required for a programme based on the DiRECT intervention are not complicated or expensive, nor is the training of routine staff burdensome. The 12-month intervention cost is less than half of the average annual UK health-care cost for a person with type 2 diabetes.[24] These considerations, and the fact that DiRECT included a high proportion of participants from more socially deprived backgrounds[15] (unlike many other programmes), all imply that the intervention should be widely transferable within routine care. Acceptability of the intervention is supported by a sustained modest improvement in quality of life.

Bariatric surgery has dominated discussions of type 2 diabetes remission, as it is an effective way of producing major weight loss and diabetes remission.[9–11] However, it is expensive and incurs risks of long-term problems such as postprandial hypoglycaemia, hypovolaemic dumping syndrome, and micronutrient deficiencies, restricting acceptability.[25,26] Additionally, many people do not wish to undergo surgery. The results of DiRECT and some previous studies[27] challenge the view that the very large weight losses targeted by bariatric surgery are essential or optimal for sustained remission of type 2 diabetes. DiRECT provides the best evidence from a real-life trial of a non-surgical approach, but research into prevention of weight regain remains underdeveloped, and improved methods will be needed to match the long-term weight-loss maintenance after surgery. Accumulated evidence points to duration of diabetes with earlier age of onset and persistent high HbA_{1c} as the main drivers of the disabling and costly clinical complications of type 2 diabetes, particularly the vascular consequences of associated hypertension and dyslipidaemia.[28] DiRECT was not powered to assess hard clinical outcomes, but seeing fewer serious adverse events in the second year of weight management is reassuring, given past anxiety about the safety of older formula diets. The findings from DiRECT for improved cardiovascular risk factors are consistent with other evidence for clinical benefits from intentional weight loss in people with type 2 diabetes.[29] The potential advantages of remission are enormous, but no long-term outcome data yet exist, other than after bariatric surgery.[9]

Our findings suggest that type 2 diabetes is a clinical consequence of accumulation of excess weight, in ectopic sites by susceptible individuals,[7] even in people with fairly low BMI. The observation of changes in liver and pancreas fat that accompany weight loss with biochemical improvements in type 2 diabetes are consistent with this understanding.[7,30] Failure to tackle the underlying process of fat accumulation seems to allow type 2 diabetes to progress. Effective long-term weight management with a resetting of long-term energy consumption is clearly essential, but other factors contribute and there remain unanswered questions and debates about dietary approaches and the optimal ratio of macronutrients. A recent study of people with type 2 diabetes has shown substantial weight loss, reduced glycaemia, and decreased medication use with a very-low-carbohydrate diet, although this study was not randomised.[31] However, meta-analyses of the controlled trial evidence show no important differences between high-carbohydrate and low-carbohydrate diets for weight control or HbA_{1c}.[32] Low-intensity support and follow-up to establish longer-term outcomes in DiRECT are currently funded to continue for all participants to a total of 3 years from baseline, and participants have consented to 5 years of follow-up. Although weight maintenance in DiRECT is better than in most previous studies, further research to optimise weight-loss maintenance is essential. This optimisation could potentially incorporate other dietary methods, as well as medications such as glucagon-like peptide-1 receptor agonists[33] or non-pharmaceutical agents such as inulin propionate ester[34] where appropriate and necessary for those who fail to maintain remissions in the long term. However, our findings make a strong case that intensive weight management should be included as a first-line option in routine care for people with type 2 diabetes to target early remission from a potentially devastating progressive disease.[18]

Some limitations and potential for bias are inevitable in research done in real-life settings. Although statisticians were masked for the analysis, participants and clinicians in DiRECT were aware of their planned allocation to the control or intervention group, since the unit of randomisation was the primary care centre (to reduce contamination between groups). With publication of the first-year results of DiRECT[12] in December, 2017, there was substantial media coverage, which might have tended to attenuate the difference between the intervention and control groups. Some participants in the control group took personal action to lose weight (nine participants in the control group lost >10 kg during the second year of the study compared with only two during the first year). Use of SGLT2 inhibitors might have increased, which could have contributed to the weight change in control participants. At 12 months, no control participants had achieved the coprimary outcome of weight loss greater than 15 kg, but at 24 months it was reached by three (2%) of 149, and there was a significant difference between the weight loss in the control group and weight gain in the intervention group. Despite this finding, the differences in remission and weight loss between groups in favour of the intervention remained highly significant and clinically important at 2 years, even though weight regain in the intervention group limited the effect size. The ethnic profile of the study population (98% white),[12] although typical of UK type 2 diabetes populations in Tyneside and Scotland, do not allow for unqualified extrapolation to other groups, such as south Asians, who tend to develop type 2 diabetes with less weight gain (and might therefore need less weight loss to undergo remission). The conclusions reported here apply to people with type 2 diabetes diagnosed

within the previous 6 years, and existing evidence has shown that remission, although still possible, is less likely after longer disease duration.[7–9] Since medication withdrawal is not part of standard guidelines, it is possible that some control participants might have been able to sustain an HbA_{1c} below the cutoff for defining remission if their antidiabetes drugs had not been withdrawn. Of those participants in the intervention group who did not achieve remission, antidiabetes drugs required to be restarted as per protocol in 51 (40%) of 129. The strengths of the study include a well defined intervention and a robust cluster-randomised study design, managed by an established clinical trials unit (Robertson Centre for Biostatistics). The study population had characteristics very similar to the general population of people with type 2 diabetes in the UK, so the results are likely to be widely generalisable.[15] The study was well powered for the coprimary outcomes of remission and weight change at the primary analysis point at 1 year and we now report clinically meaningful outcomes at 2 years. Notably, the overall loss to follow-up of 14% (41/298) over 2 years is modest for a weight-loss study in real-life conditions.[14]

In conclusion, the 2-year results of DiRECT confirm that type 2 diabetes is potentially reversible by weight loss in many cases. A structured primary care-based weight-management programme within 6 years of diagnosis can sustain remission to a non-diabetic state, off antidiabetes drugs, for more than a third of people with type 2 diabetes, with sustained remission linked to the extent of sustained weight loss.

Contributors

MEJL and RT conceived the study and are the principal investigators. All authors contributed to the design of the study. WSL is the trial coordinator and coordinated recruitment and acquisition of study data. YM coordinated the recruitment of general practices in Scotland, UK, and ACB coordinated recruitment of general practices in Tyneside, UK. NB, GT, LM, and ACB recruited participants, trained and mentored practice nurses and dietitians, and contributed to the acquisition of data. SK and IF managed the study data. AM and C-MM did the statistical analyses. PW and NS directed the biochemical analyses. CP, SZ, KGH, JCM, and AA-M contributed to the acquisition, analysis, and interpretation of mechanistic study data. HMR provided expertise on delivery of the Counterweight-Plus programme. FFS, AMR, LR, and AJA contributed to the acquisition, analysis, and interpretation of qualitative data. MEJL, RT, WSL, NS, and C-MM drafted the report. All authors critically reviewed and revised the report and have read and approved the final version.

Declaration of interests

MEJL reports research grants and personal fees for lecturing and consultancy from Novo Nordisk and consultancy fees from Counterweight Ltd, Novartis, and Eli Lilly. RT reports educational lecture fees from Eli Lilly and Novartis and advisory board fees from Wilmington Healthcare. ACB reports lecture fees from Novo Nordisk and Napp Pharmaceuticals. LM was previously employed by Counterweight Ltd and reports research funding from Cambridge Weight Plan and consultancy fees from Counterweight Ltd. GT reports funding of PhD fees and conference expenses from Cambridge Weight Plan. WSL reports conference expenses from Cambridge Weight Plan. NS reports research grants and speaker's honoraria from Boehringer Ingelheim and speaker's honoraria from Amgen, AstraZeneca, Eli Lilly, Janssen, Napp Pharmaceuticals, Novo Nordisk, and Sanofi. NB was previously employed by Counterweight Ltd and reports personal fees for freelance work and share holdings from Counterweight Ltd and funding of PhD fees and conference attendance from Cambridge Weight Plan. HMR is employed by Counterweight Ltd. All other authors declare no competing interests.

Data sharing

Deidentified data for the analyses reported in this Article, including individual participant data and a data dictionary defining each field in the set, will be made available to scientists on personal application. The study protocol and statistical analysis plan will also be made available to scientists on personal application. The data will be available from Aug 1, 2019, and provided under an agreed data access agreement. If additional download of data from the Robertson Centre for Biostatistics (University of Glasgow, Glasgow, UK) is required, a charge will be necessary. Applications for data should be made via RT (roy.taylor@ncl.ac.uk) or MEJL (mike.lean@glasgow.ac.uk).

Acknowledgments

This study was funded by Diabetes UK as a strategic research initiative (award number 13/0004691). The diet formula was donated by Cambridge Weight Plan. Neither organisation had any input into the study design, data analysis, or interpretation. We thank the NHS Primary Care Research Network and North East Commissioning Support for their support and valuable input to the study recruitment. We thank Maureen McNee, Elaine Butler, Josephine Cooney, Sara-Jane Duffus, and Philip Stewart from the University of Glasgow (Glasgow, UK) for providing technical assistance; Helen Pilkington from the Newcastle upon Tyne Hospitals NHS Foundation Trust (Newcastle upon Tyne, UK) for providing research nurse support; and Sarah Weeden and Sarah Boyle from the Robertson Centre for Biostatistics (University of Glasgow) for project and data management. We are grateful to the general practices, health-care professionals, and volunteers for their participation.

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