

5-year follow-up of the randomised Diabetes Remission Clinical Trial (DiRECT) of continued support for weight loss maintenance in the UK: an extension study



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Summary

Background In DiRECT, a randomised controlled effectiveness trial, weight management intervention after 2 years resulted in mean weight loss of 7.6 kg, with 36% of participants in remission of type 2 diabetes. Of 36 in the intervention group who maintained over 10 kg weight loss at 2 years, 29 (81%) were in remission. Continued low-intensity dietary support was then offered up to 5 years from baseline to intervention participants, aiming to maintain weight loss and gain clinical benefits. This extension study was designed to provide observed outcomes at 5 years.

Methods The DiRECT trial took place in primary care practices in the UK. Participants were individuals aged 20–65 years who had less than 6 years' duration of type 2 diabetes, a BMI greater than 27 kg/m², and were not on insulin. The intervention consisted of withdrawal of antidiabetic 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. After sharing the 2-year results with all participants, UK National Health Service data were collected annually until year 5 from remaining intervention participants who received low-intensity dietary support, intervention withdrawals, and the original randomly allocated groups. The primary outcome was remission of type 2 diabetes; having established in the DiRECT trial that sustained weight loss was the dominant driver of remission, this was assumed for the Extension study. The trial is registered with the ISRCTN registry, number 03267836.

Findings Between July 25, 2014, and Aug 5, 2016, 149 participants were randomly assigned to the intervention group and 149 were assigned to the control group in the original DiRECT study. After 2 years, all intervention participants still in the trial (101 [68%] of 149) were approached to receive low-intensity support for a further 3 years. 95 (94%) of 101 were able to continue and consented and were allocated to the DiRECT extension group. 54 participants were allocated to the non-extension group, where intervention was withdrawn. At 5 years, DiRECT extension participants (n=85) lost an average of 6.1 kg, with 11 (13%) of 85 in remission. Compared with the non-extension group, DiRECT extension participants had more visits with HbA_{1c} <48 mmol/mol (<6.5%; 36% vs 17%, p=0.0004), without glucose-lowering medication (62% vs 30%, p<0.0001), and in remission (34% vs 12%, p<0.0001). Original control participants (n=149) had mean weight loss 4.6 kg (n=82), and 5 (5%) of 93 were in remission. Compared with control participants, original intervention participants had more visits with weight more than 5% below baseline (61% vs 29%, p<0.0001), HbA_{1c} below 48 mmol/mol (29% vs 15%, p=0.0002), without antidiabetic medication (51% vs 16%, p<0.0001), and in remission (27% vs 4%, p<0.0001). Of those in remission at year 2, 26% remained in remission at 5 years. Serious adverse events in the original intervention group (4.8 events per 100 patient-years) were under half those in the control group (10.2 per 100 patient-years, p=0.0080).

Interpretation The extended DiRECT intervention was associated with greater aggregated and absolute weight loss, and suggested improved health status over 5 years.

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Introduction

Weight management programmes have been shown to reduce the progression of type 2 diabetes, improve glycaemia, and reduce the need for glucose-lowering medications.¹ The Diabetes Remission Clinical Trial

(DiRECT) found that 46% of people who had type 2 diabetes with less than 6 years' duration and were not on insulin, reach remission at 12 months, defined as HbA_{1c} below 48 mmol/mol (6.5%) without medication, using a structured weight management programme.

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See Online for appendix

Research in context

Evidence before this study

Before undertaking this study, we searched the published literature in PubMed from inception to Dec 5, 2017, for evidence on remission of type 2 diabetes using all potential interventions. For the present analysis, we reviewed new literature up to Dec 31, 2022, on evidence on remission of type 2 diabetes through weight management compared with standard medical care in diabetes clinics, searching PubMed from Dec 5, 2017, when the 12 month results of DiRECT were published, filtered for results within 5 years, and randomised clinical trials, using search terms, "type 2 diabetes remission" AND "weight loss".

We found 45 titles, of which we excluded 29 as not relevant to the present paper: one was not in humans; one was a study for obstructive sleep apnoea rather than diabetes; six were not randomised controlled trials; and 21 were results from bariatric surgery with no comparison to usual diabetes medical care.

Among the relevant publications: 11 were papers from DiRECT which are cited or considered in the discussion. Seven other publications were considered relevant to clinical benefits of weight loss for type 2 diabetes.

Added value of this study

The present study extends evidence on durability and associated benefits of weight loss and remission of type 2 diabetes following diet-induced weight loss, in answer to the top research question posed by people with type 2 diabetes in the Diabetes UK and James Lind Foundation survey (can

type 2 diabetes be cured or reversed?). Substantial weight loss is associated with sustained remission for 2 years, but weight regain is frequent. After 5 years, participants in the intervention group who continued low-intensity weight loss maintenance support beyond 2 years had a mean bodyweight 6.1 kg below baseline. Wider metabolic benefits of the intervention are also demonstrated with effective weight management on diabetes control: HbA_{1c}, blood pressure, blood lipids, and reduced medication needs. Importantly, wellbeing and quality of life, which is not often improved sustainably with weight management, were significantly better than baseline at each annual assessment.

Implications of all the available evidence

This study will add impetus to extend measures to change policies and practice for routine management of type 2 diabetes, to improve overall diabetes control, and consequently, potentially reduce or delay its complications. The dominant and very substantial effect from weight loss of 10–15 kg or more to generate remission from type 2 diabetes has now been amply demonstrated in several very different population groups, with the same mechanism including close involvement of shifts in ectopic fat. However, avoiding weight gain and regain after loss are major impediments to optimal clinical management. The need now is therefore for more intensive research to improve long-term maintenance of substantial weight loss.

At both month 12 and 24, over 80% of participants maintaining a weight loss of more than 15 kg, and 75% of those who maintained over 10 kg weight loss, were in remission of type 2 diabetes.^{2–4} Previously considered permanent and demanding life-long drug treatment, type 2 diabetes is now recognised to be a potentially reversible consequence of excessive or abnormal accumulation of body fat (ie, the disease process of obesity).⁵ The principle that ectopic fat in the liver and pancreas causes functional injury and β cell failure, which are reversible especially in the early stages,⁶ was consolidated by mechanistic studies from a DiRECT subset.^{7–9} Remission of type 2 diabetes has become accepted as an achievable management goal, with internationally agreed criteria.¹⁰

The DiRECT dietary intervention was highly cost-effective and deliverable in primary care.¹¹ Clinical guidelines have begun to recommend remission of type 2 diabetes as a key management target with interventions that incorporate the DiRECT Principles,¹² using evidence-based recommendations for weight management.¹³ The new focus on diet and remission also recognises that complications of type 2 diabetes are common, disabling, and expensive to manage, and that lives are shortened, despite modern medications.¹⁴

The DiRECT-extension study examined whether low-intensity weight loss maintenance support up to 5 years would sustain weight loss and remission, as well as improve clinical outcomes. Routinely collected UK National Health Service (NHS) data were captured for the original control group and intervention group, including withdrawals during years 1 and 2. We also considered the time spent with significant weight loss (>5% of baseline bodyweight), HbA_{1c} below 48 mmol/mol (6.5%), or in remission, as both excess weight and higher glucose exert their effects through aggregated exposure.^{15,16}

Methods

Study design and participants

DiRECT was a 2-year, open-label, cluster-randomised, controlled trial. Approvals were granted by West 3 Ethics Committee in January 2014, and the NHS health boards in Scotland and clinical commissioning groups in Tyneside (ISRCTN 03267836). The DiRECT protocol, baseline characteristics, and main results at months 12 and 24 have been published, as have secondary analyses including evaluations of predictors of remission, effects on blood pressure, mechanistic investigations, and qualitative assessments among participants and practitioners.^{2,3,7–9,17–22}

In brief, between July 25, 2014, and Aug 5, 2016, we recruited and randomly allocated 298 individuals aged 20–65 years, who were diagnosed with type 2 diabetes within the previous 6 years, were living in Scotland and northeast England, had a BMI of 27 to 45 kg/m², and who were not receiving insulin (figure 1). The intervention (Counterweight-Plus, Counterweight, London, UK) comprised withdrawal of antidiabetic and antihypertensive drugs; a total diet replacement with a nutritionally-complete formula that provided 825–853 kcal per day for 12 weeks (over 5 months to accommodate individual circumstances); stepped food reintroduction (meal-by-meal over 6 to 8 weeks); and then structured support for weight loss maintenance. A local NHS practice nurse or dietitian offered 30 min appointments every 2 weeks until food reintroduction was completed, and then monthly for maintenance. Programme-specific workbooks were provided. After the randomised trial, the 2-year results were provided to all original participants and their primary care teams, including the original controls and those who had ceased to engage, with encouragement to focus on weight control (appendix p 30). Routinely collected NHS data were gathered from patients' GP surgeries annually.

After their 2-year follow-up appointment (Sept, 2016 to July, 2018), 101 of 149 remaining intervention participants were offered continued low-intensity support (once every 3 months; appendix pp 32–33) for a further 3 years. 95 participants agreed to take part and gave written informed consent; six intervention participants withdrew at this stage. Review appointments were reduced to once every 3 months, comprising 15–30 mins with the local nurse or dietitian who had delivered the original and ongoing intervention, or a study dietitian if local health professional support was no longer possible. All study appointments were at the participants' own general practitioner (GP) practices, where participants continued to receive diabetes care and other medical care under existing current guidelines issued by The National Institute for Health and Care Excellence for NHS England, and by the Scottish Intercollegiate Guidelines Network for NHS Scotland. During COVID-19 restrictions, review appointments were conducted remotely by telephone, text, or email. Participants were asked to self-report their weight and asked to seek measurements of blood pressure and capillary blood glucose at their GP surgery if more than 5 kg weight was regained over 3 months.

Outcomes

The primary outcomes for the DiRECT extension study were bodyweight, HbA_{1c}, and other biochemistry. Clinical data (biochemistry results for lipids, liver function tests, HbA_{1c} glucose, and insulin, prescriptions and clinical events) for all original participants were obtained from NHS GP records, and included for analysis if recorded 6 months before or after the scheduled follow-up date. Extension group participants attended their GP surgery

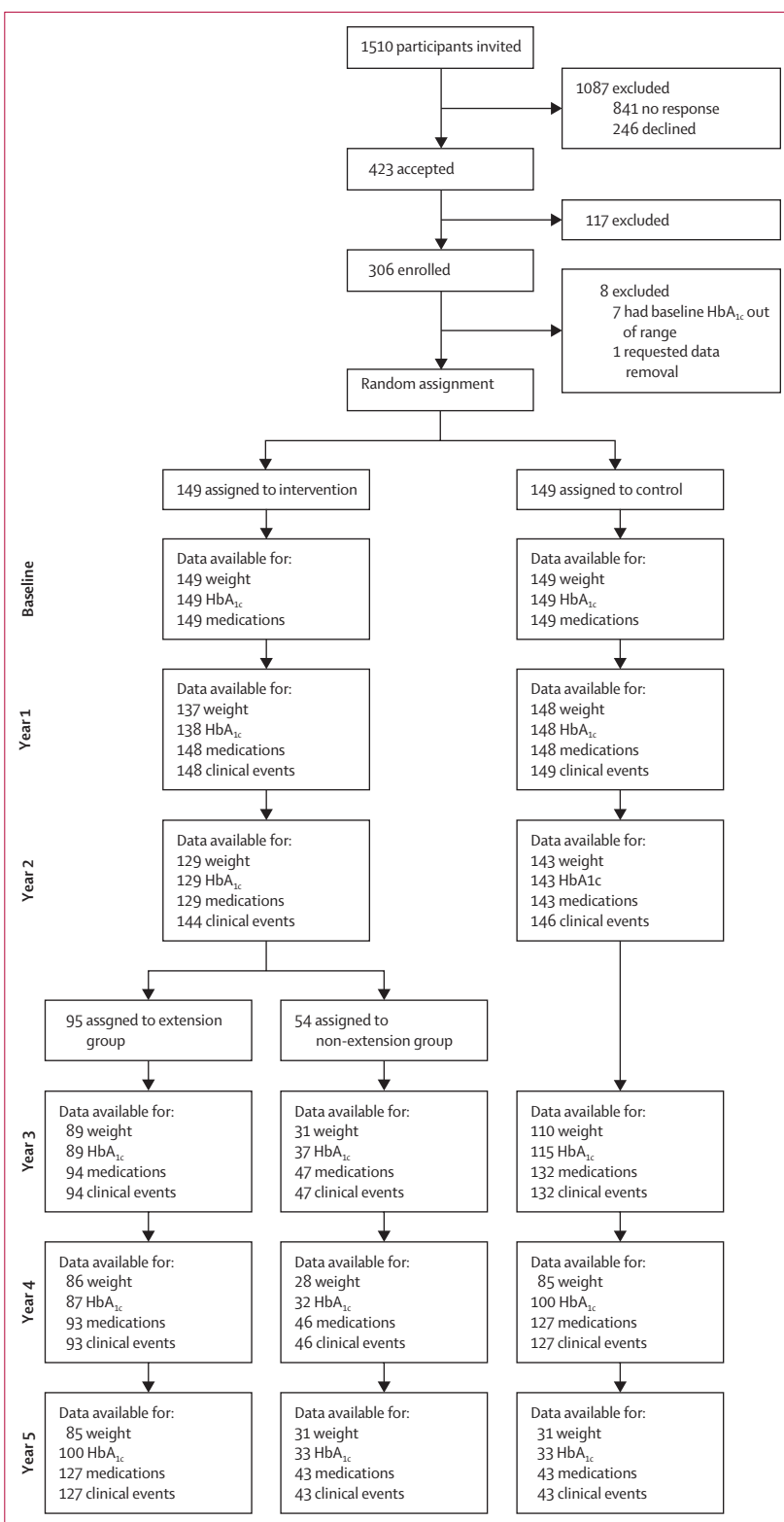


Figure 1: Trial profile

	Control vs intervention				Non-extension vs extension			
	Control (n=149)	Intervention (n=149)	Est (95% CI)	p value	Non-extension (n=54)	Extension (n=95)	Est (95%CI)	p value
Age, years	55.9 (7.3)	52.9 (7.6)	-3.0 (-4.7 to -1.3)	0.0006	49.6 (7.6)	54.8 (7.0)	5.1 (2.6 to 7.6)	0.0001
Sex								
Female	56 (38%)	66 (44%)	0.8 (0.5 to 1.2)	0.29	26 (48%)	40 (42%)	1.3 (0.6 to 2.6)	0.50
Male	93 (62%)	83 (56%)	28 (52%)	55 (58%)
Diabetes duration, years	3.0 (1.8)	3.0 (1.7)	0.1 (-0.3 to 0.5)	0.67	2.9 (1.8)	3.1 (1.6)	0.3 (-0.3 to 0.9)	0.37
Median (IQR)	2.6 (1.4 to 4.6)	3.1 (1.7 to 4.4)	3.1 (1.1 to 4.4)	3.2 (1.8 to 4.4)
BMI, kg/m ²	34.2 (4.3)	35.1 (4.5)	0.9 (-0.1 to 1.9)	0.083	35.5 (4.4)	34.9 (4.6)	-0.6 (-2.2 to 0.9)	0.40

Data are mean (SD) or n (%) unless otherwise stated. Est=estimated mean difference or odds ratio. p values and 95% CIs from two-sample T-tests, or Fisher's Exact tests.

Table 1: Baseline characteristics.

annually for study data collection, including research blood samples and quality of life was assessed using the EQ-5D-3L questionnaire. Two participants unable to attend their year 5 data collection due to COVID-19 restrictions used self-collected capillary blood HbA_{1c} kits (TDL-TINIES [BD Diagnostics, Wokingham, UK]) and self-measured weight.

Statistical analysis

Data are presented for the original randomised intervention and control groups, and within the DiRECT extension and no-extension (ie, withdrawal prior to the extension) groups. Medication data were available at 5 years for 121 (81%) of the original control group and 136 (91%) of the original intervention group. No assumptions were made regarding missing data, so remission status was calculated for participants with available data for both HbA_{1c} and medication use. Mean weight and HbA_{1c} and changes from baseline were compared between groups using t-tests. Mean values of other numeric outcomes were compared between groups using bootstrapping with 10 000 replicated datasets. Binary outcomes were compared between groups using Fisher's exact test. Data are summarised with mean differences or odds ratios between groups, 95% CIs, and p-values. Odds ratios and CIs are not reported when one group being compared had zero events. 95% CIs for selected measures (weight and change in weight, HbA_{1c} and change in HbA_{1c}, proportions off glucose-lowering medication, and proportion in remission) are also shown. Pre-specified criteria for Moderate/Major Adverse Cardiovascular Events (MMACE) and Major/Moderate Adverse Diabetes-related Events (MMADE), agreed before statistical analyses (appendix p 1) are summarised as number of events and event rate per 100 person-years of follow-up (number of years for which medication and clinical events data were available for the patient). Subgroups were compared using unadjusted negative binomial or Poisson regression (log link, variance=mean), with an offset term for logarithm of person-years of follow-up. Model choice was based on the Akaike information

criterion. Incidence rate ratios between groups are summarised in tabular form, with 95% CIs, and p-values. Where no events occurred in one of the groups under comparison, Fishers Exact test p-values are reported.

As global measures of outcomes over the 5 years, making no assumptions about timepoints with missing data, we calculated the percentage of available follow-up times (ie, the number of annual follow-ups when the characteristic was observed, divided by the number of follow-ups with data available) that each participant spent with: first, weight at more than 5% below baseline, second, HbA_{1c} below 48 mmol/mol (<6.5%), third, off all antidiabetic medications, and fourth, in remission (HbA_{1c} <48 mmol/mol (<6.5%) without glucose-lowering medications). As a sensitivity analysis, we also analysed these global measures assuming that they were not achieved for intervening time-points with missing data by counting the number of follow-up time points at which each condition was met and dividing by five.

The DiRECT extension group was self-selected by remaining engaged with the intervention at 2 years. Furthermore, control group participants were strongly encouraged to control their weight after the end of the 2-year randomised trial, so their outcomes do not reflect usual care. Consequently, differences between groups beyond the 2-year point might not reflect intervention. The original DiRECT trial was powered to detect a difference in remission rates at 1 year, not differences in longer-term or other outcomes.

Statistical analyses were done with R version 4.0.4 and presented descriptively, with multiple unadjusted two-group comparisons to highlight any patterns of differences over time. The presence or absence of statistical significance between subgroups should be interpreted cautiously. We have not applied adjustments for multiple comparisons, nor used any strict threshold as indicating statistical significance. Analyses of weight and HbA_{1c} at each follow-up were repeated using mixed effects linear regression model allowing for clustering at the general practice level: results were very similar

	Control vs intervention					Intervention: non-extension vs extension						
	Control		Intervention		Est (95% CI)	p value	Non-extension		Extension		Est (95%CI)	p value
	N	Summary	N	Summary			N	Summary	N	Summary		
Weight, kg												
Baseline	149	98.8 (16.1)	149	101.0 (16.7)	2.2 (-1.5 to 6.0)	0.25	54	103.8 (17.6)	95	99.5 (16.1)	-4.3 (-10.1 to 1.5)	0.14
Year 1	148	97.7 (16.4)	137	90.4 (16.4)	-7.3 (-11.1 to -3.5)	0.0002	42	97.3 (17.0)	95	87.4 (15.2)	-10.0 (-16.1 to -3.9)	0.0017
Year 2	143	96.4 (16.3)	129	93.2 (17.2)	-3.2 (-7.2 to 0.8)	0.12	34	101.1 (18.4)	95	90.4 (15.9)	-10.7 (-17.8 to -3.5)	0.0042
Year 3	110	94.7 (17.5)	120	95.1 (16.7)	0.3 (-4.1 to 4.8)	0.89	31	102.1 (19.0)	89	92.6 (15.2)	-9.6 (-17.2 to -2.0)	0.015
Year 4	85	95.5 (17.2)	114	93.5 (14.8)	-2.0 (-6.6 to 2.6)	0.39	28	94.6 (14.6)	86	93.2 (15.0)	-1.3 (-7.8 to 5.1)	0.67
Year 5	82	96.4 (17.2)	116	94.6 (16.4)	-1.9 (-6.7 to 2.9)	0.45	31	98.3 (18.6)	85	93.2 (15.3)	-5.1 (-12.7 to 2.4)	0.18
Weight change, kg												
Year 1	148	-1.0 (3.7)	137	-10.0 (8.0)	-9.0 (-10.5 to -7.5)	<0.0001	42	-5.3 (6.8)	95	-12.1 (7.6)	-6.8 (-9.4 to -4.2)	<0.0001
Year 2	143	-2.3 (5.2)	129	-7.6 (6.5)	-5.3 (-6.7 to -3.9)	<0.0001	34	-3.7 (5.0)	95	-9.1 (6.4)	-5.4 (-7.5 to -3.2)	<0.0001
Year 3	110	-3.8 (5.6)	120	-6.4 (6.5)	-2.6 (-4.1 to -1.0)	0.0016	31	-5.4 (8.0)	89	-6.7 (5.9)	-1.3 (-4.4 to 1.8)	0.41
Year 4	85	-3.7 (6.8)	114	-5.4 (5.8)	-1.7 (-3.5 to 0.1)	0.066	28	-3.6 (6.9)	86	-5.9 (5.3)	-2.3 (-5.2 to 0.6)	0.12
Year 5	82	-4.6 (6.1)	116	-5.6 (5.8)	-1.1 (-2.8 to 0.6)	0.21	31	-4.4 (7.2)	85	-6.1 (5.2)	-1.6 (-4.5 to 1.2)	0.25
HbA_{1c}, mmol/mol												
Baseline	149	58.2 (11.5)	149	60.4 (13.7)	2.2 (-0.6 to 5.1)	0.13	54	65.0 (16.8)	95	57.8 (10.8)	-7.1 (-12.2 to -2.1)	0.0063
Year 1	148	59.6 (12.1)	138	50.6 (13.3)	-9.0 (-11.9 to -6.0)	<0.0001	43	58.9 (15.2)	95	46.8 (10.4)	-12.0 (-17.1 to -6.9)	<0.0001
Year 2	143	58.6 (14.4)	129	54.4 (15.9)	-4.2 (-7.8 to -0.6)	0.024	34	66.5 (16.7)	95	50.1 (13.2)	-16.3 (-22.7 to -10.0)	<0.0001
Year 3	115	62.4 (16.0)	126	62.2 (19.2)	-0.3 (-4.8 to 4.2)	0.90	37	69.9 (21.0)	89	58.9 (17.5)	-10.9 (-18.8 to -3.1)	0.0071
Year 4	100	64.1 (15.7)	119	63.1 (16.8)	-0.9 (-5.3 to 3.4)	0.67	32	71.4 (19.2)	87	60.1 (14.8)	-11.4 (-18.9 to -3.8)	0.0041
Year 5	93	64.4 (16.0)	118	66.7 (19.3)	2.3 (-2.5 to 7.1)	0.35	33	77.1 (22.9)	85	62.7 (16.1)	-14.5 (-23.2 to -5.7)	0.0018
HbA_{1c} change, mmol/mol												
Year 1	148	1.4 (11.6)	138	-9.6 (15.4)	-11.0 (-14.1 to -7.8)	<0.0001	43	-6.5 (18.7)	95	-11.0 (13.6)	-4.4 (-10.7 to 1.9)	0.17
Year 2	143	0.4 (15.5)	129	-5.2 (16.4)	-5.6 (-9.4 to -1.8)	0.0043	34	1.7 (19.4)	95	-7.7 (14.5)	-9.4 (-16.7 to -2.1)	0.013
Year 3	115	4.2 (15.6)	126	2.5 (19.4)	-1.7 (-6.2 to 2.8)	0.45	37	3.9 (24.2)	89	1.9 (17.2)	-2.0 (-10.8 to 6.7)	0.64
Year 4	100	7.0 (15.2)	119	4.1 (16.7)	-3.0 (-7.2 to 1.3)	0.17	32	7.4 (21.9)	87	2.9 (14.3)	-4.5 (-12.9 to 3.9)	0.28
Year 5	93	5.9 (15.5)	118	6.9 (17.4)	1.0 (-3.5 to 5.5)	0.66	33	10.4 (24.3)	85	5.5 (13.8)	-4.9 (-13.9 to 4.2)	0.29

Summaries are mean (SD). Est=estimated mean difference. P-values and CIs from two-sample T-tests.

Table 2: Weight and HbA_{1c} over time

(as with all previous analyses of DiRECT, implying a high fidelity of intervention delivery), so analyses reported here do not adjust for clustering.

Role of the funding Source

The funder of the study had no role in study design, data collection, analysis, interpretation, or writing of the report.

Results

Between July 25, 2014, and Aug 5, 2016, 149 participants were randomly assigned to the intervention group and 149 were assigned to the control group in the original DiRECT study. At 2 years, 101 (68%) of 149 participants were still engaged with the intervention and were approached to receive low-intensity support for a further three years. 95 (94%) of 101 were able to continue and consented and constitute the DiRECT extension group. The remaining 54 participants from the original intervention group, who had withdrawn at different stages, make up the non-extension group. Follow-up data were sought for all participants, but some patients did not have data at certain timepoints,

as shown in figure 1. Baseline characteristics are presented in table 1. We report observed data without assumptions about outcomes with missing data, thus numbers and remission rates differ slightly from previous publications from DiRECT.

Summaries of weight measurements and changes from baseline are shown in table 2, figure 2A, and the appendix (p 24). In the extension intervention group, mean weight fell by 12.1 kg (SD 7.6) during year 1, increased at year 2 compared with year 1, but stabilised and remained 6.1 kg (SD 5.2) below baseline at year 5. While 28 (78%) of the 36 intervention group participants who had maintained over 10 kg weight loss at 2 years were in remission (table 3), at 5 years 21 participants were over 10 kg below baseline bodyweight, and three (14%) of them were in remission.

Weight and HbA_{1c} were available for 82 (55%) and 93 (62%) respectively in controls, and for 116 (78%) and 118 (79%) in the intervention group. The DiRECT extension group had weight recorded for 85 (89%) at 5 years, compared to 31 (57%) in the non-extension group, and HbA_{1c} available for 85 (89%) versus 33 (61%). Mean HbA_{1c} in

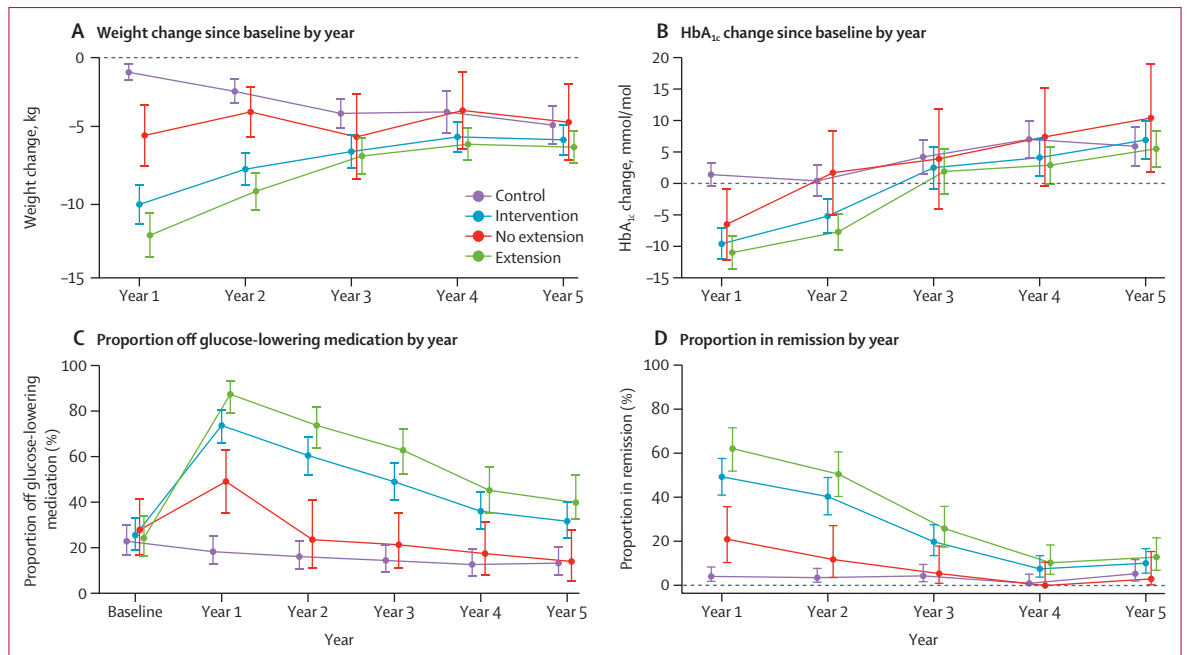


Figure 2: Mean weight in kg (A) HbA_{1c} in mmol/mol (B) changes since baseline, proportions of those off all glucose-lowering medications (C) and in remission each year (D)

Data points are not aligned with actual year for readability.

the extension intervention group fell by 11.0 mmol/mol (after withdrawing glucose-lowering medications) during year 1, then rose, reaching 5.5 mmol/mol above baseline at year 5 (table 2, appendix pp 24–25).

The proportion of participants off glucose-lowering medications was 87% (83 of 95) at year 1 and 40% (37 of 93) at year 5 (table 4, figure 2C). One DiRECT extension group participant started semaglutide in year 3, and two were receiving insulin at year 5 (appendix p 2).

At year 1, 59 (62%) of 95 DiRECT extension participants with data were in remission; this declined to 11 (13%) of 85 participants with data at year 5 (table 4). 48 (51%) of 95 participants were in remission at year 2 (figure 2D); 43 of these 48 participants were also followed up at 5 years, and 11 (26%) remained in remission, with average weight loss 8.9 kg (median 7.3 kg) for those who were in remission at years 2 and 5.

Over the 5-year follow-up period, extension participants had a mean of 69% follow-up assessments with weight more than 5% below baseline, 36% of follow-up assessments with an HbA_{1c} below 48 mmol/mol, and 62% of follow-up visits off glucose-lowering medication (table 5). Overall, DiRECT extension participants were in remission for a mean of 34% of follow-up assessments. These results were similar in sensitivity analyses, with 32% in remission, and weight more than 5% below baseline, HbA_{1c} below 48 mmol/mol, and off glucose-lowering medications at 64%, 33%, and 61% respectively, treating visits with missing data as not having achieved the improved health status (appendix p 7). Weight regain, and loss of remission,

were both common, although of the 32 people with weight data who lost remission between year 2 and year 5, seven (22%) saw a weight reduction over this period, and an additional ten (31%) had small increases of less than 1 kg per year.

Mean blood pressure in the DiRECT extension group, 135/82 mm Hg at year 5, was similar to the DiRECT baseline, with 44 (47%) of 93 not receiving antihypertensive medications. After an initial drop in systolic blood pressure up to year 2 (despite fewer people taking medications), systolic blood pressure returned to baseline levels (mean change from baseline at year 5: 1.9 [95% CI -2.4 to 5.7] mm Hg, $p=0.37$; appendix pp 3). At baseline, 43 (45%) of the 95 DiRECT extension group participants were not taking antihypertensive medications. This rose to 68 (72%) of 95 at year 1, but fell to 44 (47%) of 93 at year 5 (table 4). About a quarter (13 of 51) of DiRECT extension participants on antihypertensive medications at baseline remained off medications at year 5, while a quarter (11 of 42) of those not receiving antihypertensive medications at baseline had started treatment by year 5. Numbers of other medication prescriptions increased from mean 3.2 per participant at baseline to 4.3 per participant at year 5, $p<0.0001$, appendix p 2).

Measured in the intervention group only, sustained reductions in insulin and γ -glutamyl transferase as well as increases in HDL-cholesterol were noted over the 5 years, and alanine transaminase and C-reactive protein were below baseline values for 2 years. Total cholesterol rose over the 5 years. EQ-5D visual analogue scale values

were significantly higher than baseline at each of the five annual assessments (appendix p 3–6).

Participants who did not take part in The DiRECT extension ($n=54$) had similar mean baseline weight to DiRECT extension participants (103.8 kg vs 99.5 kg, $p=0.14$), but slightly higher baseline mean HbA_{1c} (65.0 mmol/mol vs 57.8 mmol/mol, $p=0.0063$; table 2). People in the non-extension group had a lesser response to the intervention (mean weight loss at year 1: 5.3 kg vs 12.1 kg, $p<0.0001$; mean HbA_{1c} reduction 6.5 mmol/mol vs 11.0 mmol/mol, $p=0.17$); table 2, figure 2A). Fewer non-extension participants were off glucose-lowering medications at year 1 than those in the DiRECT extension group (26 [49%] of 53 vs 83 [87%] of 95); and at year 2 (8 [24%] of 34 vs 70 [74%] of 95; both $p<0.0001$), resulting in lower likelihood of remission (table 4). Four non-extension participants (12%) were in remission at the end of year 2, and one (3%) at year 5 (table 4).

The percentage of follow-up visits with weight more than 5% below baseline was lower for non-extension participants than DiRECT extension participants (45% vs 69%, $p<0.0001$). Similarly, fewer follow-up assessments showed HbA_{1c} under 48 mmol/mol in the non-extension group (17% vs 36%, $p=0.0004$; table 5). These differences appear driven by the first 2 years of the study: during years 3 to 5, the non-extension group only had marginally fewer years with weight over 5% below baseline and HbA_{1c} <48 mmol/mol, compared to the DiRECT extension group (appendix p 8; $p=0.10$ and 0.30 respectively). Nevertheless, non-extension participants had significantly fewer visits off glucose-lowering medication, and in remission, over the whole 5 years (table 5), and during the extension phase (appendix p 8).

Antihypertensive prescriptions in the non-extension group at year 5 (mean 1.0 medication per participant) were similar to baseline within-group (mean 0.9, $p=0.53$) and also similar to the DiRECT extension group at year 5 (mean 0.9, $p=0.54$; table 4).

After the initial substantial weight loss during year 1, the DiRECT intervention group had progressive, but incomplete, weight regain. Following exposure to the randomised controlled trial results after 2 years, when all original participants were encouraged to lose weight, there was modest weight loss in the control group (table 2, figure 2A). Control participants were 5% below baseline weight for only 29% of 5 year follow-up assessments, compared with 61% for intervention participants ($p<0.0001$, table 5). The two centres (Scotland with dietitian or practice nurse delivery and Tyneside, England, with practice nurse delivery) had similar results for the main outcomes (appendix p 10).

Managed under NHS best practice clinical guidelines, HbA_{1c} rose gradually in the control group. In the intervention group HbA_{1c} was significantly lower than in control group participants up to year 2, but not in

	Control	Intervention
Year 1		
Weight loss >10 kg since baseline	2/148 (1%)	61/134 (46%)
In remission, of those with weight loss >10 kg since baseline	0/2	46/61 (75%)
Year 2		
Weight loss >10 kg since baseline	9/141 (6%)	36/129 (28%)
In remission, of those with weight loss >10 kg since baseline	0/9	28/36 (78%)
Year 3		
Weight loss >10 kg since baseline	8/105 (8%)	25/119 (21%)
In remission, of those with weight loss >10 kg since baseline	0/8	11/25 (44%)
Year 4		
Weight loss >10 kg since baseline	11/83 (13%)	18/110 (16%)
In remission, of those with weight loss >10 kg since baseline	0/11	3/18 (17%)
Year 5		
Weight loss >10 kg since baseline	13/76 (17%)	21/113 (19%)
In remission, of those with weight loss >10 kg since baseline	1/13 (8%)	3/21 (14%)

There are minor differences between this paper and previous publications in the numbers in remission, because one individual with HbA_{1c} close to the cut-off at year 2 was classified differently using both HbA_{1c} diagnostic criteria (<48 mmol/mol and <6.5%) in the current paper, compared with classification using only one criterion in previous publications.

Table 3: Remission outcomes with bodyweight loss of over 10 kg at each year to year 5, in participants originally randomised to the DiRECT intervention or control groups

subsequent years (table 2, figure 2B). However, intervention participants had twice as many visits as controls with HbA_{1c} <48 mmol/mol (29% vs 15%), despite considerably fewer receiving glucose-lowering medications (68% vs 87% at year 5; tables 4, 5).

In the control group, only 11 individuals (7%) achieved remission at any annual study assessment, and five (5%) of 93 were in remission at year 5, with a mean weight loss of 4.6 kg (tables 2, 3). Known remissions in the original intervention group were 68 (49%) of 138, 52 (40%) of 129, 25 (20%) of 126, 9 (8%) of 119, and 12 (10%) of 118 at years 1 to 5 respectively, with mean weight loss at year 5 of 5.6 kg (SD 5.8; tables 2, 3).

In the intervention group only, glucose-lowering medications and antihypertensive medications were withdrawn at baseline, and thereafter recommenced according to protocols for elevated glycaemia or blood pressure. The intervention group was prescribed fewer glucose-lowering drugs than the control group (mean 1.3 vs 1.6, $p=0.028$), and marginally fewer antihypertensive medications (mean 1.0 vs 1.2, $p=0.085$; table 4) at year 5, and intervention group participants spent significantly more of follow-up time off glucose-lowering medications (51% vs 16%; table 5). Blood pressure was not measured in the control group after year 2, but only 42 (35%) remained off antihypertensive medications at year 5 compared with 62 (46%) in the intervention group.

Other medications are shown in the appendix (p 2). Prescriptions of other medications tended to be lower in the intervention group, though without statistical significance at any single time point. Statin treatment

	Control vs intervention					Intervention: non-extension vs extension						
	Control		Intervention		Est (95% CI)	p value	Non-extension		Extension		Est (95% CI)	p value
	N	Summary	N	Summary			N	Summary	N	Summary		
Number of glucose-lowering medications												
Baseline	149	1.1 (0.8)	149	1.1 (0.9)	0.1 (-0.1 to 0.3)	0.53	54	1.2 (1.0)	95	1.1 (0.9)	-0.1 (-0.4 to 0.3)	0.70
Year 1	148	1.3 (0.9)	149	0.4 (0.7)	-0.9 (-1.1 to -0.7)	<0.0001	53	0.8 (0.9)	95	0.1 (0.4)	-0.6 (-0.9 to -0.4)	<0.0001
Year 2	143	1.3 (1.0)	129	0.6 (0.9)	-0.7 (-1.0 to -0.5)	<0.0001	34	1.3 (0.9)	95	0.4 (0.7)	-0.9 (-1.3 to -0.6)	<0.0001
Year 3	132	1.4 (0.9)	141	0.9 (1.0)	-0.5 (-0.7 to -0.3)	<0.0001	47	1.4 (1.0)	94	0.6 (0.9)	-0.8 (-1.2 to -0.5)	<0.0001
Year 4	127	1.5 (0.9)	139	1.1 (1.0)	-0.4 (-0.6 to -0.1)	0.0024	46	1.5 (1.0)	93	0.9 (1.0)	-0.5 (-0.9 to -0.2)	0.0040
Year 5	121	1.6 (1.0)	136	1.3 (1.2)	-0.3 (-0.6 to 0.0)	0.028	43	1.7 (1.1)	93	1.1 (1.1)	-0.6 (-1.0 to -0.2)	0.0036
Off glucose-lowering medications												
Baseline	149	34 (23%)	149	38 (26%)	1.2 (0.7 to 2.0)	0.68	54	15 (28%)	95	23 (24%)	0.8 (0.4 to 1.9)	0.70
Year 1	148	27 (18%)	148	109 (74%)	12.4 (7.0 to 22.7)	<0.0001	53	26 (49%)	95	83 (87%)	7.1 (3.0 to 17.7)	<0.0001
Year 2	143	23 (16%)	129	78 (60%)	7.9 (4.4 to 14.8)	<0.0001	34	8 (24%)	95	70 (74%)	8.9 (3.4 to 25.9)	<0.0001
Year 3	132	19 (14%)	141	69 (49%)	5.7 (3.1 to 10.8)	<0.0001	47	10 (21%)	94	59 (63%)	6.2 (2.6 to 15.7)	<0.0001
Year 4	127	16 (13%)	139	50 (36%)	3.9 (2.0 to 7.8)	<0.0001	46	8 (17%)	93	42 (45%)	3.9 (1.6 to 10.7)	0.0014
Year 5	121	16 (13%)	136	43 (32%)	3.0 (1.5 to 6.2)	0.0006	43	6 (14%)	93	37 (40%)	4.0 (1.5 to 12.9)	0.0028
Number of antihypertensive medications												
Baseline	149	1.0 (1.1)	149	1.0 (1.2)	0.0 (-0.2 to 0.3)	0.75	54	0.9 (1.1)	95	1.1 (1.2)	0.2 (-0.2 to 0.5)	0.37
Year 1	148	1.0 (1.0)	148	0.5 (0.7)	-0.6 (-0.8 to -0.4)	<0.0001	53	0.5 (0.8)	95	0.4 (0.7)	-0.1 (-0.4 to 0.1)	0.36
Year 2	143	1.1 (1.1)	129	0.7 (0.9)	-0.3 (-0.6 to -0.1)	0.0052	34	0.9 (0.9)	95	0.7 (0.9)	-0.2 (-0.6 to 0.1)	0.24
Year 3	132	1.1 (1.1)	141	0.8 (1.0)	-0.3 (-0.6 to -0.1)	0.0052	47	0.9 (1.1)	94	0.7 (1.0)	-0.2 (-0.5 to 0.2)	0.32
Year 4	127	1.2 (1.1)	139	0.8 (1.0)	-0.3 (-0.6 to -0.1)	0.0068	46	0.9 (1.1)	93	0.8 (1.0)	-0.1 (-0.5 to 0.2)	0.50
Year 5	121	1.2 (1.1)	136	1.0 (1.1)	-0.2 (-0.5 to 0.0)	0.085	43	1.0 (1.1)	93	0.9 (1.1)	-0.1 (-0.5 to 0.3)	0.54
Off antihypertensive medications												
Baseline	149	68 (46%)	149	68 (46%)	1.0 (0.6 to 1.6)	1.00	54	25 (46%)	95	43 (45%)	1.0 (0.5 to 2.0)	1.00
Year 1	148	57 (39%)	148	101 (68%)	3.4 (2.1 to 5.7)	<0.0001	53	33 (62%)	95	68 (72%)	1.5 (0.7 to 3.3)	0.27
Year 2	143	57 (40%)	129	68 (53%)	1.7 (1.0 to 2.8)	0.03	34	13 (38%)	95	55 (58%)	2.2 (0.9 to 5.4)	0.071
Year 3	132	49 (37%)	141	73 (52%)	1.8 (1.1 to 3.0)	0.02	47	22 (47%)	94	51 (54%)	1.3 (0.6 to 2.9)	0.48
Year 4	127	43 (34%)	139	69 (50%)	1.9 (1.1 to 3.3)	0.01	46	22 (48%)	93	47 (51%)	1.1 (0.5 to 2.4)	0.86
Year 5	121	42 (35%)	136	62 (46%)	1.6 (0.9 to 2.7)	0.098	43	18 (42%)	93	44 (47%)	1.2 (0.6 to 2.8)	0.58

(Table 4 continues on next page)

	Control vs intervention						Intervention: non-extension vs extension					
	Control		Intervention		Est (95% CI)	p value	Non-extension		Extension		Est (95% CI)	p value
	N	Summary	N	Summary			N	Summary	N	Summary		
(Continued from previous page)												
Percentage of follow-up times off anti-hypertensive medication	149	37.0 (45.9)	148	54.7 (45.6)	17.7 (7.2 to 28.0)	0.0006	53	51.7 (47.2)	95	56.4 (44.8)	4.8 (-10.8 to 19.9)	0.54
In remission												
Year 1	148	6 (4%)	138	68 (49%)	22.7 (9.3 to 67.4)	<0.0001	43	9 (21%)	95	59 (62%)	6.1 (2.5 to 16.2)	<0.0001
Year 2	142	5 (4%)	129	52 (40%)	18.3 (7.0 to 61.2)	<0.0001	34	4 (12%)	95	48 (51%)	7.6 (2.4 to 31.8)	0.0001
Year 3	115	5 (4%)	126	25 (20%)	5.4 (1.9 to 18.8)	0.0003	37	2 (5%)	89	23 (26%)	6.0 (1.4 to 55.7)	0.0073
Year 4	100	1 (1%)	119	9 (8%)	8.0 (1.1 to 358.0)	0.023	32	0 (0%)	87	9 (10%)	NA	0.11
Year 5	93	5 (5%)	118	12 (10%)	2.0 (0.6 to 7.5)	0.31	33	1 (3%)	85	11 (13%)	4.7 (0.6 to 210.9)	0.17

Data are mean (SD) or n (%) unless otherwise stated. Estimate and 95% CI not shown for binary measures with zero events in one group. p-values and 95% CIs for mean differences derived from bootstrapping with 10 000 replicated datasets. Est=estimated mean difference or odds ratio. NA=not applicable.

Table 4: Use of glucose-lowering, antihypertensive medications, and remission status over time.

was not addressed by study protocol, but the proportion using statins was significantly lower in the intervention group than control group, with odds ratios of approximately 0.5 at every follow-up visit. For weight loss medications at year 5, no participants in either group were prescribed orlistat; GLP-1 agonist medications were prescribed to four (3%) participants in the control group and three (2%) participants in the intervention group, and GLP-1 agonist medications to four in the control group and three in the intervention group.

Adverse clinical events collected from clinical records are shown in the appendix (pp 11–12). The incidence of serious adverse events (SAEs) in the intervention group was under half that of the control group (event rate 4.8 per 100 person-years vs 10.2 per 100 person-years, incidence rate ratio 0.5 (95% CI 0.3–0.8), $p=0.0080$), and similar for the DiRECT extension and non-extension groups (4.7 vs 5.0 per 100 person-years [100_{p,y}], incidence rate ratio 0.9). There were no significant differences for numbers with MMACE or MMADE (appendix p 12). In the control group, the difference in SAEs compared with the intervention group was driven by more bacterial infections and eight newly diagnosed cancers (two colon, two prostate, one each of pancreas, lung, kidney, and bladder). In the intervention group, just one cancer (lung) developed in a participant who had withdrawn before their diagnosis.

Clinical events over years 2 to 5, in relation to the treatment objectives to enhance health and wellbeing (to reduce weight, reduce use of glucose-lowering and antihypertensive medications, to reduce HbA_{1c} to <48mmol/mol, and to induce remission), are

summarised in the appendix separately for the original control and Intervention arms (pp 13–14). Clinical events during each single year, and cumulative event rates at each annual assessment point are presented (appendix pp 15–22). Patients who met treatment objectives at year 1 in the intervention group generally had fewer MMADEs during the subsequent 4 years (12.8 vs 23.0 per 100_{p,y} for those who did or did not reaching >5% weight loss at 1 year; 11.0 vs 19.6 per 100_{p,y} for reaching HbA_{1c} <48 mmol/mol; 13.5 vs 20.0 per 100_{p,y} for being off glucose lowering medication; and 11.1 vs 19.1 per 100_{p,y} for being in remission (appendix pp 13–14). Our sensitivity analysis on global measures produced very similar results, and our conclusions were unchanged.

Discussion

The main purpose of the DiRECT extension study was to evaluate a 5-year structured weight management programme, designed to enable patients to reach and remain in remission, entirely within routine primary care. The fall in remission rate was disappointing, when related to the high figure of 36% at year 2 for the entire DiRECT intervention group, but in relation to usual outcomes under current routine management the 5-year results (known remissions in 11 (13%) of those with data, or 7% of the original 149 intervention group) remain remarkable. The Look AHEAD trial, with a far more intensive intervention, reported 11% remissions at year 1, and 7% at year 4 in a group with longer duration diabetes.²¹ Overall, the original DiRECT intervention group had well-sustained

	Control vs intervention				Non-extension vs extension			
	Control (149)	Intervention (149)	Est (95% CI)	p-value	Non-extension (54)	Extension (95)	Est (95%CI)	p-value
Weight loss >5%								
N	149	143	32 (24-39)	<0.0001	48	95	24 (12-36)	<0.0001
Mean (SD)	29% (31)	61% (35)	45% (35)	69% (32)
Median (IQR)	25% (0-50)	60% (33-100)	37% (20-69)	80% (40-100)
HbA_{1c} <48 mmol/mol								
N	149	144	15 (8-22)	0.0002	49	95	19 (8-29)	0.0004
Mean (SD)	15% (27)	29% (33)	17% (30)	36% (33)
Median (IQR)	0% (0-20)	20% (0-50)	0% (0-25)	25% (0-60)
Off all glucose-lowering medication								
N	149	148	35 (26-43)	<0.0001	53	95	32 (19-45)	<0.0001
Mean (SD)	16% (33)	51% (41)	30% (39)	62% (37)
Median (IQR)	0% (0-0)	50% (0-100)	20% (0-40)	60% (30-100)
In remission								
N	149	144	23 (17-29)	<0.0001	49	95	23 (12-32)	<0.0001
Mean (SD)	4% (14)	27% (33)	12% (27)	34% (34)
Median (IQR)	0% (0-0)	20% (0-40)	0% (0-0)	25% (0-60)

p-values and 95% CIs from bootstrapping with 10 000 replicated datasets. Est=estimated mean difference or odds ratio.

Table 5: Global clinical outcomes from the DiRECT intervention, according to percentage of follow-up times based on available follow-up times for each participant over 5 years

mean weight loss, especially the DiRECT extension subgroup (6.1 kg at year 5), far more than usual under conventional type 2 diabetes care.²⁴ After the 2-year results were provided to all participants and primary care teams, including the original control and drop-out (non-extension) groups, with encouragement to focus on weight control (appendix pp 31–32), weight changes and HbA_{1c} became more similar in the two originally randomised groups (although a 1.6 kg weight loss, the observed difference, could be considered a treatment success over 5 years, as reported in other studies), but the number of prescribed medications was lower, and frequency of remission higher, in the intervention group. Most control participants stayed on glucose-lowering medication, and few attained remission, with no requirement for a therapeutic trial of medication withdrawal. Withdrawal of medication is welcomed by people with type 2 diabetes, but some medications, notably statins, do confer medical benefit even without type 2 diabetes.

Lower weight, lower HbA_{1c}, and type 2 diabetes remission, were reached earlier and persisted longer in the original intervention group than in the control group participants, particularly in the extension study. Consequently, aggregated exposure to clinically significant weight loss (>5% of body weight), or being in remission, as a percentage of visits (indicator of follow-up time), were much greater in intervention than control participants (61% vs 29% and 27% vs 4%, respectively). The same was true for not receiving glucose-lowering medication, and intervention participants also

spent a higher percentage of time by visit with HbA_{1c} below 48 mmol/mol. Collectively, such findings would predict favourable long-term outcomes for people with type 2 diabetes. The study was not powered to demonstrate between-group differences in MMACE or MMADE events, and neither reached p<0.05 over the 5 year period, but SAEs in the intervention group were half those in controls. Those in the intervention arm who lost over 5% of their weight at year 1 tended to have fewer MMADE events over the remainder of the study period. In the whole original intervention group, reaching HbA_{1c} below 48 mmol/mol (<6.5%) during the first year was associated with fewer MMADEs thereafter (appendix p 13). The same was true for those in the intervention group who reached remission at year 1, versus not achieving remission at year 1. The data suggest that stopping diabetes medications is safe, and possibly beneficial, when undergoing effective weight management.

The mean 6.1 kg weight loss at 5 years was attained over the COVID-19 pandemic and studies have shown that the pandemic was associated with weight gain in the general population.²⁵ The restrictions also curtailed the planned 15–30 min review appointments, impeding relapse management when weight regain occurred. Weight regain remains the major impediment to sustained remission. Participants in the DiRECT extension group cited stresses related to employment and social factors as affecting their ability to adhere to behaviours required to maintain weight loss, and some ceased to attend appointments.²⁴ DiRECT was

not designed to explore factors behind weight loss maintenance in detail, but a rise in ghrelin predicted weight regain.²¹ Intervention participants were advised regularly to increase physical activity, but they demonstrated no net increase, and physical activity was not related to weight change or remission during the first 2 years.²⁶ Research is needed to establish methods to overcome the physiological adaptations and external factors which drive weight regain.^{27,28}

It is important not to interpret the group differences reported as treatment effects, or to assume all were causal. The DiRECT extension participants were around 5 years older than the non-extension group, most of whom withdrew from the intervention early in DiRECT, but the extension participants had lower weight and lower baseline HbA_{1c}, and showed larger early responses to the intervention. The non-extension group showed greater rises in HbA_{1c} and less weight loss to year 2, and during years 2 to 5 had larger HbA_{1c} increases than those who continued into the extension. Remission rates broadly followed weight changes in the DiRECT extension and intervention groups, but were noticeably lower in the control group despite a mean year 5 weight loss of 4.6 kg. Explanations might include continuing glucose-lowering medication despite remission (seven control participants had HbA_{1c} <48 mmol/mol but remained on medication at year 5), a cumulative area under the curve effect which benefitted earlier weight loss in the intervention group, or more frequent unintentional weight loss through illness in the control group: while weight loss correlated with a fall in HbA_{1c} at every year in the intervention group, no such relationship was seen in the control group, suggesting differences in causality (appendix pp 25–29).

The DiRECT extension study results over years 3–5 are necessarily observational, since it was decided a priori that the control group, randomly allocated to usual care, should not be deprived of an effective treatment. This probably reduced subsequent differences between intervention and control groups during follow-up to year 5. Patient-reported outcomes will be particularly important for future research. Quality of life, using EQ-5D-3L showed a gratifying improvement above baseline at each annual visit up to year 5 (appendix pp 3), and we previously reported positive patient-reported outcomes from the first 2 years of DiRECT from formal qualitative assessments.²¹

Reaching remission is an important new management target, achievable by many people living with type 2 diabetes. The programme used in DiRECT, in routine primary care, is clearly effective, but prolonged remission was infrequent. Relapse of type 2 diabetes was most likely with weight regain over the subsequent 2 to 3 years, but many relapsed by year 5 with modest weight regain. Weight regain allows liver and pancreas fat to re-accumulate in individuals who had previously developed type 2 diabetes, revealing their metabolic syndrome predisposition to accumulate ectopic fat with

age and weight gain.²⁹ Longer term data are not yet available, but redistribution of body fat into ectopic sites occurs with ageing,^{30,31} possibly even without weight regain, particularly likely since even after losing 10–15 kg, many participants still had a BMI above 30 kg/m². The risk of type 2 diabetes rises with BMI over 23 kg/m² in people of European origin,³² or at lower BMI with Asian ancestry,³³ with increased liver and pancreas fat, even at BMI levels below 25 kg/m², which have become accepted as normal or a so-called healthy BMI.³⁴ Additionally, loss of glucose-oxidative muscle mass (through inactivity or chronic inflammation) promotes type 2 diabetes at lower weights in older age, when a stable body weight probably reflects gain of adipose tissue.³⁵

While bariatric surgery has established that long-term type 2 diabetes remission is possible for many, with reduced clinical events,^{36,37} no non-surgical clinical trials have reported longer results than DiRECT.³⁸ With only 3 years average duration of diabetes, mean age 54, and most participants on statins, event rates for cardiovascular outcomes would be predictably modest.¹⁵ Genetic data confirm clinical observations linking higher BMI to some important diabetes outcomes (eg, heart failure and renal failure),³⁹ and observational follow-up of larger, longer, trials increasingly suggest benefits from substantial intentional weight loss, likely related to blood pressure control.^{40,41} Weight loss provided potent antihypertensive effect initially,¹⁸ but prescriptions of antihypertensive medications rose as weight was regained. At year 5, blood pressure remained close to baseline, and we also noted lower CRP, insulin levels, and ALT, in keeping with lower liver fat in the intervention group (appendix pp 3–6). Taken together, these findings indicate a more favourable metabolic health status in those randomly allocated to the intervention, and there was some evidence of associations between freedom from pre-specified MMADE events and meeting intervention outcomes during the first year (appendix pp 13–14). There are many possible confounding factors, and low statistical power, but these results should provide an incentive to improve interventions, and for larger, longer observational studies into the effects of remission on the clinical outcomes of people with type 2 diabetes.

DiRECT has strengths from the representativeness of the population studied and the robust objective clinically relevant data reported. However, interpretation of data beyond the 2 years randomised controlled trial has uncertainties and several limitations and potential sources of bias are discussed in the methods. The DiRECT extension study was conducted in routine primary care, with minimal additional resources, and many outcomes of potential interest could not be measured. Although the groups were well matched for baseline characteristics,⁴² those who continued into the DiRECT extension were probably more health-aware

than the non-extension group, with different health behaviours, and thus might have had some advantageous characteristics for greater 1 year weight losses. The DiRECT extension group attended more follow-up appointments, either in-person or remotely during the COVID-19 pandemic. The DiRECT extension group was older than the non-extension (55 vs 50 years), potentially predicting more SAEs and clinical events, however they had fewer clinical events. We report observational differences, so not necessarily causal, recognising that some control group participants undertook intentional weight loss (four participants on semaglutide at year 5), and engagement varied within the intervention group, but protection from clinical events is consistent with known patterns in causal risk factors (eg, blood pressure, glycaemia, lipids) with weight loss.

Given the multiple potential sources of bias, we report the data without adjustments and without imputation of missing data, aiming to present the data openly, and to interpret them with caution, recognising that some confounding could affect associations. With small numbers of events, particularly within single years, estimated associations may be subject to sparse data bias,⁴³ so can only be considered approximate.

The DiRECT trial addressed the top research priority from people with diabetes, which is to achieve remission of type 2 diabetes.⁴⁴ Remission effect-sizes at years 1 and 2,^{2,3} also shown in the DIADEM-1,⁴⁵ and in the STANDby⁴⁶ randomised trials, with almost identical weight management interventions, are large and consistent, so likely generalisable. The same applies to type 2 diabetes with BMI well below the cutoff used for obesity (above 30 kg/m², or 27 kg/m² in Asian populations).³³ Key assumptions in the original economic analysis proved over-conservative: participants' weights did not all return to baseline with no remissions after 5 years, thus cost-savings might be greater.¹¹ The financial cost of type 2 diabetes care is extremely high, and cost-effectiveness analysis using the DiRECT 2-year data showed that the intervention would become dominant (ie. saving more than it cost) after 5 years. However our results underscore the difficulty people have maintaining intentional weight loss in an obesogenic environment.⁴⁷ Future obesity research, specifically weight loss maintenance, requires funding which reflects costs incurred by multi-morbidities mediated by obesity.⁴⁸ Trained, sympathetic, support such as phone calls by a primary care physician, and active relapse management, can help prevent weight regain, and remote delivery and digital support methods using widely available technology need exploration.^{48,49} The present 5-year results from DiRECT, coupled with long-term follow-up of people who achieved type 2 diabetes remission in the LookAHEAD trial,⁵¹ provide observational encouragement that weight management may help to delay or avoid clinical complications of diabetes. Not all people will succeed with purely dietary

intervention, but the new and highly effective GLP-1 agonists and related agents offer additional support for weight management if they are affordable. Combining them with a DiRECT principles weight management programme could provide more opportunities to reduce the burden of type 2 diabetes.

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 oversaw recruitment and acquisition of study data. YM coordinated the recruitment of general practices in Scotland and ACB coordinated recruitment of practices in Tyneside. NB, GT, LM, ACB, TK, and KI recruited participants, trained, and mentored practice nurses and dietitians, and contributed to the acquisition of data. AM and AMcC did the statistical analyses. PW and NS directed the biochemical analyses. CP, SZ, KGH, and JCM, contributed to the acquisition, and analysis, of mechanistic study data, and to final data interpretation. FFS, and AJA contributed to the acquisition and analysis of qualitative data, and to final data interpretation. MEJL, RT, WSL, NS, and AMcC drafted the manuscript. All authors critically reviewed and revised the manuscript and have read and approved the final version.

Declaration of interests

MEJL reports grants and personal fees unconnected with the present work from Counterweight, Novo Nordisk, Novartis, and Eli Lilly. RT has received lecture fees from Novartis and Eli Lilly, and has served on an advisory panel for Wilmington Healthcare. NB reports employment and shareholding in Counterweight, and PhD fees funded by Cambridge Weight Plan (outside the submitted work). GT received funding for PhD fees and conference attendance from Cambridge Weight Plan outside the submitted work. WSL reports support for conference attendance from Cambridge Weight Plan outside the submitted work. NS reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics; and personal fees from Abbott Laboratories, Amgen, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novo Nordisk, Pfizer, and Sanofi, outside the submitted work. LM reports employment by Counterweight during the conduct of study, was previously a shareholder in Counterweight, and previous employment from Cambridge Weight Plan outside the submitted work. All other authors declare no competing interests.

Data sharing statement

The raw data will be made available on request, once the current and planned analyses are completed.

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