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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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Two-year results of the randomised Diabetes Remission Clinical Trial (DiRECT)

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Tables 2; Figures 3

CONSORT FORM

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Research in Context

Evidence before this study

Before undertaking this study, the authors searched the published literature in PUBMED for evidence on remissions of type 2 diabetes, using all potential interventions. For the present analysis, the authors reviewed new literature on remissions of type 2 diabetes through weight management, searching PUBMED since publication of the 12 month results of DiRECT (December 2017) using search terms: clinical trial, remission, type 2 diabetes, weight loss. The search revealed 8 titles, of which only 3 indicated weight loss interventions. Two of these were to DiRECT, and one to results from laparoscopic surgery, which was deemed not relevant.

Added Value of this study

The present study extends to 2 years evidence for durable remissions of type 2 diabetes following diet-induced weight loss. Wider benefits relating to blood pressure, blood lipids, and well-being are demonstrated. It provides an increasingly confident answer to the top research question posed by people with type diabetes in the Diabetes UK/James Lind Alliance survey (published in The Lancet 2017): 'Can type 2 diabetes be cured or reversed?'

Implications of all the available evidence

This study will provide added impetus to extend the early measures already announced to change existing NHS policy and practice for the routine management of type 2 diabetes. The present data, and other relevant data on diabetes control, HbA1c and weight management all point towards the likelihood that intensive weight management has the potential to reduce or delay complications of diabetes and improve clinical outcomes.

ABSTRACT

Background: DiRECT reported diabetes remission at one year for 46% of participants allocated to an integrated structured weight management programme. We now assess two-year findings.

Methods: DiRECT is an open-label, cluster-randomised, controlled trial in primary care practices randomised to a weight management programme (intervention) or best-practice care by guidelines (control). We recruited individuals aged 20–65 years, with <6 years duration of type 2 diabetes, body-mass index 27–45 kg/m^2, and not receiving insulin. The intervention comprised withdrawal of anti-diabetes and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet) for 12-20 weeks, stepped food reintroduction (2–8 weeks), and then structured support for weight loss maintenance. Co-primary outcomes, analysed hierarchically, were weight loss ≥15 kg, and remission of diabetes, defined as HbA_{1c} <6·5% (<48 mmol/mol) with no anti-diabetes medications.

Findings: At 24 months, 53/149 (35·6%) of those commencing the intervention and 5/149 (3·4%) in the control group (adjusted odds ratio 25·8, 95% CI 8·3,80·8; p<0·0001) had remission, and 11·4% of intervention and 2·0% of the control group (adjusted odds ratio 8·2 (2·2,30·0), p=0·0015) had weight loss ≥15kg. Of those maintaining ≥10kg weight loss (45/272), 64% (29/45) achieved remission, and 24.2% (36/149) of the intervention group maintained ≥10kg weight loss. Adjusted mean differences between groups were, in changes in body weight -5·4 kg, (-6·9,-4·0), p<0·0001, in HbA1c -4·8 mmol/mol, (-8·3,-1·4), p=0·0063 despite >50% fewer anti-diabetes agent use in intervention group, and SBP -3·4 mmHg, (-6·7,-0·2), p=0·0397. Serious adverse events were similar at 12 months, but fewer occurred in intervention than control in the second year (9 vs. 22). Quality of life improved more from baseline in the intervention than the control group, adjusted mean difference 4·6 (0·4,8·9, p=0·032).

Interpretation: This programme sustained remissions at 24 months for over a third of people with type 2 diabetes. Weight loss of ≥10 kg provides remission for two thirds**.**

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Introduction

The Diabetes Remission Clinical Trial (DiRECT) demonstrated that almost half (46%) of a group with type 2 diabetes up to 6 years duration could achieve remission at 12 months, by following a structured weight management programme [1], and for 86% of those in the intervention group who achieved target weight loss of 15kg or more. These results have changed perceptions of a condition previously assumed to be permanent and demanding life-long drug treatment. Between one in 16 to 1 in 10 adults in the UK and US, respectively have type 2 diabetes [2,3], with much higher rates (up to 1 in 5) in other parts of the world[4]. Diabetes complications are common and expensive to manage so associated healthcare costs are enormous despite the improvements offered through application of clinical guidelines. It 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.[5]

The extreme strength of association between excess weight gain in adult life and type 2 diabetes makes a causal relationship 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 ectopic fat within the liver and pancreas in susceptible individuals, has now been consistently observed. [6–8] Several studies have now shown that weight loss of at least 10-15 kg frequently normalises blood glucose in people with short-duration type 2 diabetes, and DiRECT did this in a real-life primary care setting. [9-12]

The major current questions are whether remissions can be durable and delivered at scale to reach the large numbers of patients, in primary care where they are usually managed, and then the extent to which vascular complications of diabetes can be delayed or avoided. Sufficient weight loss for remission, of over 10-15 kg, can be achieved in various ways, including bariatric surgery but also using a low-calorie formula for total diet replacement. The key issue now is how best to support long term maintenance of weight loss and remissions of diabetes. This is the greatest problem faced

by individuals, and still misunderstood and requiring specific research, as in the past formula diets were 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, stepped food reintroduction with emphasis on energy balance, and then structured support for weight loss maintenance with provision for relapse management. We now report the clinical outcomes in the intervention and control groups at two years.

Methods

Study design and participants

DiRECT is a two-year open-label, cluster-randomised controlled trial. Ethics approval was granted by West 3 Ethics Committee in January, 2014, with approvals by the National Health Service (NHS) Health Boards in Scotland and Clinical Commissioning Groups in Tyneside. The trial is registered with the ISRCTN registry, number 03267836.

The protocol, including details of recruitment methods, study conduct, and planned analyses, has been published elsewhere,[14] as have the baseline characteristics of the groups.[15] In brief, between 2014-2016, we recruited individuals aged 20–65 years, diagnosed with type 2 diabetes within the past 6 years, body-mass index 27–45 kg/m^2, and not receiving insulin. The intervention programme (Counterweight-Plus), delivered entirely within a routine primary care setting by a trained NHS dietitian or nurse (as available locally), comprised total diet replacement (825–853 kcal/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. For the maintenance phase up to 24 months, participants were offered monthly 30 minute appointments with the dietitian or practice nurse, using tailored workbooks. In the event of weight regain >2kg, participants were offered a ‘rescue plan’ of 2-4 weeks partial meal replacement, and if >4kg a total

diet replacement and food reintroduction, with the offer of orlistat treatment. Advice to increase daily physical activity was reinforced at each visit although no specific targets were set. Both anti-diabetic and antihypertensive drugs were withdrawn on day 1 of total diet replacement, with protocols for their reintroduction if necessary, according to clinical guidelines. Antihypertensive drugs were withdrawn to avoid postural hypotension, as blood pressure generally decreases upon commencing a low energy diet.[8] All participants provided written informed consent for the two-year study.

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 medication 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 co-primary outcomes were a reduction in weight of 15 kg or more, and remission of diabetes, defined as HbA_{1c} less than 6·5% (<48 mmol/mol),[18,19] from baseline to month 24. Secondary outcomes were quality of life, as measured by the EuroQol 5 Dimensions (EQ-5D-3L); serum lipids; and physical activity. Other pre-specified outcomes included programme acceptability, sleep quality, blood pressure, and serious adverse events collected from GP records, as detailed in the trial protocol.[14] We additionally assessed changes in medications as exploratory outcomes. Outcome data were collected at baseline and repeated at 12 and 24 months as planned. All pre-specified outcomes are reported with the exception of exercise and sleep data which are not yet analysed.

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

Statistical analysis

The planned primary analyses were done at the individual level, according to the intention-to-treat principle. The co-primary outcomes were analysed in a hierarchical manner, the weight loss outcome first, with no adjustment of the p-values for multiple comparisons. For participants who did not attend the 12 or 24 month study assessment, and for whom data could not be obtained from GP records, we made the assumption that the primary outcomes were not met. For the main analysis of secondary outcomes, no assumptions were made regarding missing data.

Sample-size calculations indicated 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 one 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 intra-class correlation coefficient of 0·05 to account for cluster randomisation, and an estimated dropout rate of 25% within 12 months.

Outcomes were compared between groups with mixed-effects regression models, with adjustment for GP practice as a random effect. Logistic models were used for binary outcomes, and Gaussian models for continuous outcomes. If possible, models were adjusted for the minimisation variables (study centre and practice list size), age, sex, duration of diabetes and HbA1c 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 tried. For serum triglyceride, groups were compared with a linear regression model of log-transformed values, with adjustment for baseline log triglyceride.

For continuous outcomes, model fit was assessed visually with normal probability plots. When substantial departure from a normal distribution was observed, groups were also compared with non-parametric Wilcoxon or 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.

Role of the funding source

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

Results

We recruited 306 individuals from 49 intervention (n=23) and control (n=26) practices, and the intention-to-treat population comprised 149 participants per group (Figure 1). Baseline characteristics were similar between groups.[15]

A total of 116/149 (77·9%) participants in the intervention and 140/149 (94·0%) in the control group attended the 24 month study assessment, thus overall 42/298 (14·1%) randomised participants did not attend at 24 months. The baseline characteristics of those who attended this visit compared with those who did not are shown in Table S1. Additional data for weight and HbA1c were obtained from GP records where available, such that data at 24 months for body weight and for HbA1c were available for 272 (91·3%) participants (n=129 intervention and n=143 control). For the intention-to-treat analysis, the remaining 26 participants with no data at 24 months, who did not attend the 12 or 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 monthly appointments during the second year (9·6 in those who attended the two-year follow-up visit).

At 24 months, weight loss of 15 kg or more was observed in 17/129 (13·2%) intervention group participants (17/149, 11·4% of those commencing the intervention), and by 3/149 participants in the control group (adjusted odds ratio 7·49, 95% CI 2·05-27·32, p=0·0023, missing values imputed; Figure 2A). In the intervention group 24.2% (36/149) maintained ≥10kg weight loss at 24 months. Absolute weight at each time point is shown in Table 1.

At 24 months, without imputing missing data and assuming no remission for those without data, diabetes was in remission in 53/129 (41·1%) participants in the intervention group (35·6% of 149 commencing the intervention) and 5/149 (3·4%) in the control group (adjusted odds ratio for imputed outcome 25·82, 95% confidence interval (8·25, 80·84); p<0·0001). (Figure 2B).

For the entire study population, remissions at 24 months were achieved by 8/154 (5.2%) participants who failed to achieve 5 kg weight loss, 21/73 (28·8%) who maintained 5–10 kg loss, 15/25 (60·0%) who maintained 10–15 kg loss, 29/45 (64·4%) who maintained ≥10kg loss, and 14/20 (70·0%) of participants who lost 15 kg or more (Figure 2C). Four participants (out of 50 with weight gain (8·0%)) were in remission at both 12 and 24 months despite small weight gains (0-2kg) at 24 months. These individuals all had baseline Hba1c between 6.5% and 6.63%. Post-hoc analyses were conducted on the change in weight by achieved remission at each time point (Figure S1) and the baseline characteristics of those attending the 24 months visit compared with those who did not (Table S1).

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

Between 12 and 24 months, mean body weight increased by 2·6 kg (SD 5·0) in the intervention group and decreased by 1·3 kg (SD 4·2) in the control group (adjusted difference in weight change between groups of 3·34 kg, 95% CI 2·18 to 4·50; p<0·0001). In the intervention group, those maintaining remission between 12 and 24 months (n=48), after having lost on average 15·51 kg (6·6) during year 1, regained on average 4·25 kg, SD 3·68. In those who relapsed after 12 months (n=15) weight regain was greater (7·09 kg (SD 5·42), t-test p=0·0732), after having lost an average of 11·98 kg (SD 7·7). The group not in remission at 12 months (n=62 with weight data at both 12 and 24 months) had an average weight gain of 0.26 kg (SD 4.7) after having lost 5·81 (SD 6·4) at 12 months. Over the 24 months from baseline, those who maintained remission lost an average of 10·4 kg (SD 6·8), those who were in remission at 12 months but relapsed at 24 months lost 3·7 kg (SD 5·9) and those who did not achieve remission at 12 or 24 months lost 3·2 (5·2) kg (Figure S1). Out of 143 intervention arm participants who have data during treatment phases, about half required relapse management with brief total diet replacement and the offer of orlistat during the two years: 71 (49·7%) had not had any 'rescue plan', 49 (34·3%) had one, 15 (10·5%) had two and 8 (5·6%) had three or more rescue plan phases. The numbers of intervention arm participants receiving orlistat at 12 and 24 months were 0 and 3 respectively. As the mean baseline weight was close to 100kg, similar patterns were recorded for BMI and for weight change expressed as a percentage of baseline weight.

In the control group, mean HbA1c remained similar between baseline (58·2 mmol/mol, SD 11·5) and 24 months (58·6, SD 14·4), with 115/149 (77·2%) receiving anti-diabetes medications at baseline, increasing to 120/143 (83·9%) at 24 months. In the intervention group, mean HbA1c fell between baseline (60·4, SD 13·7) and 24 months (54·4, SD 15·9), adjusted mean difference -4·82, (-8·28, -

1·36), p=0·0063, with 111/149 (74·5%) receiving anti-diabetes medications at baseline and 51/129 (39·5%) at 24 months.

Mean systolic blood pressure at 24 months decreased by 1·4 mmHg (SD 13·4) in the control group and by 4·3 mmHg (SD 18·7) in the intervention group (adjusted mean difference -3·43, (-6·70, -0·16), p=0·0397), with 86/143 (60·1%) in the control group but only 61/129 (47·3%) in the intervention group receiving antihypertensive medication at 24 months (adjusted odds ratio 0·31, (0·14, 0·71), p=0·0058)(Table 1).

Serum triglycerides at 24 months decreased below baseline values by 0·2 mmol/l (SD 0·7) in the control group and by 0·4 mmol/l (SD 1·2) in the intervention group (adjusted mean difference in log-transformed values -0·14 (-0·23, -0·04), p=0·0055).

Total serious adverse events reported for the first 24 months of DiRECT were 15 in the intervention and 25 in the control group, in 11 and 19 participants respectively. While there had been no significant difference at 12 months, in the second year of DiRECT, six participants in the intervention group and 16 in the control group suffered nine and 22 serious adverse events respectively. None led to withdrawal from the study. The serious adverse events (Table 2) included several vascular events in the control arm (two cerebral vascular accidents, one toe amputation, one aortic aneurysm rupture, and one sudden death), compared with one non-fatal MI in the intervention group in a person who had not attended for review. Two other serious adverse events, both in one participant during year one (cholelithiasis, abdominal pain), were deemed potentially related to the intervention.

Quality of life assessed by visual analogue score at 24 months improved more in the intervention group (change from baseline 10·0 (0·0, 20·0) than in controls 2·5 (-5·0, 9·0); p=0·03)). The absolute scores are shown in Table 1.

In the whole study population, likelihood of remission at 24 months (n=58/298, 19.5%) was higher for male sex (adjusted odds ratio for female vs. male 0·44 (0·22, 0·88), p=0·0196), and increased with age (adjusted odds ratio 1·08 (1·03, 1·13) per year, p=0·0020), , with weight loss from baseline (adjusted odds ratio 0·83 (0·77, 0·90) per kg, p<0·0001), and with weight-change from 12 to 24 months (adjusted odds ratio per kg gained 1.11 (1·03, 1·21), p=0·0103). Likelihood of remission at 24 months was not influenced by baseline BMI (adjusted odds ratio per kg/m^2 0·99 (0·92, 1·06), p=0·7701) or duration of diabetes within the 6-year range included (adjusted odds ratio per year 0·92 (0·76, 1·11), p=0·3949). Where this could be assessed, the effects did not differ significantly between intervention and control group (p for interaction: sex p=0·3136, weight change from 12 to 24 months p=0·4682, duration of diabetes within the 6 year range studied p=0·1144). All models were adjusted for treatment, practice list size, centre and a random effect for practice.

Discussion

The two-year results of DiRECT demonstrate that type 2 diabetes of up to 6 years' duration is not necessarily a permanent, lifelong, condition. Indeed, it is reversible to a durable remission, over 24 months, for 64% of those who maintain a weight loss of over 10kg, and for 70% with weight loss >15kg. The evidence-based structured weight management programme, delivered by routine primary care staff in a community setting, achieved remissions at two years for over a third of those who commenced the intervention, and over 40% of those with two-year data. Achieving and maintaining weight loss is clearly the dominant factor behind remission of type diabetes, and participants reverting to diabetes between 12 and 24 months regained more weight than those maintaining remission. Weight regain was less than in many published studies[13] but remains a challenge: the ambitious co-primary outcome of >15kg weight loss was maintained by only 11.4% by intention to treat analysis, down from 24% at 1 year. Blood pressure, lipids and quality of life improved with the intervention. 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

the past anxiety over safety of older formula diets. The overall diabetes-related cardiometabolic risk profile improved, with reduced lipids and fewer participants requiring antihypertensive medications to control blood pressure than in the control group.

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, focussing from the outset on the need for long-term maintenance of weight loss. The observed weight regain and remission rates compare favourably with Look AHEAD[20], which delivered an intensively supported programme in specialist US diabetes centres, combining considerable increases in physical activity and dietary programmes. Losing over 10kg in Look Ahead was associated with reduced cardiovascular events in a post hoc analysis. Remission of type 2 diabetes was not the primary outcome in Look Ahead, but was observed in 9·2% at 2 years, with average weight loss of a little under 6kg.[21] The DiRECT intervention has similarities with Look Ahead, but was designed specifically for achieving remissions, with a view to delivery at scale for the very large numbers of people with type 2 diabetes, therefore 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 comparable to those reported using the same programme in a prospective audit of its routine use in other primary care and community settings, which found similar results for people with and without diabetes.[22] The resources required for a programme based on the DiRECT intervention are not complicated or expensive, nor the training of routine staff burdensome. The 12-month intervention cost is under half of the average annual UK healthcare cost of a person with type 2 diabetes.[23] These considerations, and the fact that DiRECT included a high proportion of participants from more socially deprived backgrounds [15] (unlike many other programs), all imply that the intervention should be widely transferable within routine

healthcare. Acceptability of the intervention is supported by a sustained modest, statistically significant improvement in quality of life.

Bariatric surgery has dominated discussions of type 2 diabetes remission as an effective way of producing major weight loss and diabetes remissions.[10–12] However, it is expensive and incurs risks of long-term problems, such as post-prandial hypoglycaemia, hypovolaemic dumping syndrome and micronutrient deficiencies that restrict acceptability.[24,25] In addition, many people do not wish to undergo surgery. The results of DiRECT and some previous studies[26] 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 elevation of HbA1c as the main drivers of the disabling and costly clinical complications of type 2 diabetes, in particular the vascular consequences of associated hypertension and dyslipidaemia.[27] The present observations on these improved cardiovascular risk factors are consistent with other evidence for clinical benefits from intentional weight loss for people with type 2 diabetes[28].The potential advantages of remission are enormous but no long-term outcome data yet exist, other than after bariatric surgery. [9]

The present results suggest that type 2 diabetes is a clinical consequence of accumulation of excess weight, in ectopic sites by susceptible individuals, [17] even with a relatively low body mass index. The observation of changes in liver and pancreas fat which accompany weight loss with biochemical improvements in type 2 diabetes are consistent with this.[29,8] It appears that failure to tackle that underlying process of fat accumulation allows 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 demonstrated

substantial weight loss, reduced glycaemia and decreased medications with a very low carbohydrate diet, although this was not randomised.[30] However, meta-analyses of the controlled trial evidence show no important differences between high and low carbohydrate diets for weight control or HbA1c.[31] 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. While weight maintenance in DiRECT is better than in most previous studies, further research to optimise weight loss maintenance is essential. This could potentially incorporate other dietary methods, and medications if individually required, such as GLP-1 agonists[32] or non-pharmaceutical agents like inulin propionate ester [33] where appropriate and necessary for those who fail to maintain remissions long-term. The present results 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 seek early remission from a potentially devastating progressive disease.[18]

Some limitations and potential for bias are inevitable in research conducted in real-life settings. Although statisticians were blinded for the primary analysis, participants and clinicians in DiRECT were aware of their planned allocation to the control or intervention group, as the unit of randomisation was the primary care centre, to reduce contamination between groups. Following publication of the first-year results of DiRECT (December 2017[1]) there was considerable media coverage which may have tended to attenuate the difference between the randomised groups. A proportion of the control group took personal action to lose weight (9 participants in the control group lost >10 kg during the second year compared to 2 during the first year). Increased use of SGLT-2 inhibitors may also have contributed to the weight change in controls. At 12 months no control participants had achieved the co-primary outcome of weight loss greater than 15kg, but at 24 months it was reached by 3 (2·1%), and there was a significant difference between the weight loss in the control group and weight gain in the intervention group. Despite this the differences in

remission and weight loss between groups were still highly significant and clinically important at 2 years. Weight regain in the intervention group contributed to limit the effect size. The racial and ethnic characteristics, while typical of UK type 2 diabetes populations, do not allow for unqualified extrapolation to other groups, such as South Asians, who tend to develop diabetes with less weight gain (and may 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, though still possible, is less likely after longer durations of disease.[8,10] As medication withdrawal is not part of standard guidelines, it has to be considered that some control participants might have been able to sustain HbA1c below the cut off for remission if their anti-diabetic agents had been withdrawn. The strengths of the study include a well-defined intervention and a robust cluster-randomised study design, managed by a well-established clinical trials unit. The sample had characteristics very similar to the general population of people with type 2 diabetes, so the results are likely to be widely generalisable.[15] The study was well powered for the co-primary outcomes of remission and weight change at the primary analysis point at 1 year and we now observe clinically meaningful outcomes at 2 years. Relating to this, the overall loss to follow up of 14·1% 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 most cases. A structured primary care weight management programme within 6 years of diagnosis can sustain remission to a non-diabetic state, off anti-diabetes drugs, for over a third of people with type 2 diabetes and over two thirds of those who lost more than 10kg at 24 months.

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 (GPs) in Scotland and ACB coordinated recruitment of GP practices in Tyneside. 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 CMM 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 CMM drafted the manuscript. All authors critically reviewed and revised the manuscript, and have read and approved the final version.

Declaration of interests

MEJL reports personal fees from Counterweight Ltd, grants and personal fees from Novo Nordisk, personal fees from Novartis, personal fees from Eli Lilly, other from Cambridge Weight Plan, outside the submitted work. IF reports grants from Diabetes UK, during the conduct of the study. RT reports other from Eli Lilly, other from Novartis, other from Wilmington Healthcare, outside the submitted work. ACB reports personal fees from Novo Nordisk, personal fees from Napp Pharmaceuticals, outside the submitted work. LMcC reports other from Counterweight Ltd, during the conduct of the study; other from Cambridge Weight Plan, personal fees from Counterweight Ltd, outside the submitted work. GT reports other from Cambridge Weight Plan, outside the submitted work. WSL reports other from Cambridge Weight Plan, outside the submitted work. JCM reports grants from Diabetes UK, during the conduct of the study. SK reports grants from Diabetes UK charity, during the conduct of the study. NS reports personal fees from Amgen, personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, personal fees from Eli Lilly, personal fees from Janssen, personal fees from NAPP Pharmaceuticals, personal fees from Novo Nordisk, personal fees from Sanofi, outside the submitted work. CMM reports grants from Diabetes UK, during the conduct of the study. NB reports other from Counterweight Ltd, during the conduct of the study; other from

Cambridge Weight Plan, grants and other from British Dietetic Association, outside the submitted work. SK reports grants from Diabetes UK, during the conduct of the study. AMcC reports grants from Diabetes UK, during the conduct of the study. HMR reports other from Counterweight Ltd, during the conduct of the study. All other authors declare no competing interest.

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Legends to Figures

Figure 1: Trial profile

Figure 2: Primary outcomes and remission of diabetes in relation to weight loss at 12 and at 24 months. Regression models adjusting for practice list size, study centre and a random effect for practice.

A: First co-primary outcome, achievement of ≥15kg weight loss, by randomised group. **B:** Second co-primary outcome, remission of diabetes (HbA_{1c} <48mmol/mol, off anti-diabetic medication for 2 months), by randomised group.
C: Remission of diabetes, in relation to weight loss achieved (both randomised groups combined).

Figure 3: Changes in weight of participants who remained in the trial and those who dropped out during each phase of the intervention.

Error bars represent 95% CI

Figure S1: Median weight change shown by remission status. Error bars represent interquartile range.

Table 1: Key Secondary and other outcomes

		N[(c)]	Mean (SD)				Intervention Effect at 24 months			ICC
			Baseline	12 months	24months	Change @ 24 months	Estimate	95% CI	p-value	
Secondary Outcomes										
Weight (kg)	Intervention	129	101·0 (16·7)	90·4 (16·4)	93·2 (17·2)	-7·6 (6·5)	-5·43	(-6·87, -3·99)	p<0·0001	<0·01
	Control	143	98·8 (16·1)	97·7(16·4)	96·4 (16·3)	-2·3 (5·2)				
HbA1c (mmol/mol)	Intervention	129	60·4 (13·7)	50·6(13·3)	54·4 (15·9)	-5·2 (16·4)	-4·82	(-8·28, -1·36)	p=0·0063	<0·01
	Control	143	58·2 (11·5)	59·6(12·1)	58·6 (14·4)	0·4 (15·5)				
HbA1c (%)	Intervention	129	7·7 (1·3)	6·8(1·2)	7·1 (1·5)	-0·5 (1·5)	-0·44	(-0·76, -0·13)	p=0·0063	<0·01
	Control	143	7·5 (1·1)	7·6(1·1)	7·5 (1·3)	0·0 (1·4)				
Number of prescribed oral antidiabetic medications[(a)]	Intervention	129	1·1 (0·9)	0·4(0·7)	0·6 (0·9)	-0·6 (0·8)	-0·86	(-1·02, -0·69)	p<0·0001	<0.01
	Control	143	1·1 (0·8)	1·3(0·9)	1·3 (1·0)	0·3 (0·6)				
Number of prescribed antihypertensive medications	Intervention	129	1·0 (1·1)	0·5(0·7)	0·7 (0·9)	-0·3 (0·9)	-0·36	(-0·53, -0·19)	p<0·0001	0·03
	Control	143	1·0 (1·1)	1·0(1·0)	1·1 (1·1)	0·1 (0·5)				
Systolic blood pressure (mmHg)	Intervention	113	132·7 (17·5)	133·0(16·3)	130·3 (13·6)	-4·3 (18·7)	-3·43	(-6·70, -0·16)	p=0·0397	0·01
	Control	140	137·2 (16·0)	135·8(14·6)	135·4 (14·0)	-1·4 (13·4)				
EQ-5D Health Utility Score	Intervention	113	0·798 (0·288)	0·793(0·278)	0·819 (0·268)	-0·002 (0·205)	0·024	(-0·021, 0·070)	p=0·2949	<0·01
	Control	140	0·802 (0·281)	0·759 (0·302)	0·788 (0·253)	-0·013 (0·194)				
Quality of Life	Intervention	113	65·8 (19·1)	73·7(19·0)	75·2 (17·3)	8·2 (20·1)	4·64	(0·39, 8·89)	p=0·0324	0·04

EQ-5D VAS	Control	140	72·1 (19·6)	69·1(15·6)	74·0 (16·8)	1·7 (15·1)				
Other Outcomes										
Triglycerides (mmol/l) [(b)]	Intervention	105	2·1 (1·4)	1·7 (1·4)	1·6 (1·0)	-0·4 (1·2)	-0·14	(-0·23, -0·04)	p=0·0055	<0.01
	Control	138	1·9 (0·9)	2·0 (1·2)	1·7 (0·9)	-0·2 (0·7)				
Binary outcomes			N (% of all available at this time point)				Odds Ratio	95% CI	p-value	
Number on any anti-diabetic medications	Intervention	129	111 (74·5%)	39 (26·4%)	51 (39·5%)		0·03	(0·01, 0·08)	p<0·0001	
	Control	143	115 (77·2%)	121 (81·8%)	120 (83·9%)					

Intervention effects reported as estimated mean differences (Intervention-Control), based on mixed effects linear regression model, adjusted for randomised group, baseline value, age, sex, duration of diabetes and HbA1c at baseline, study centre (Tyneside, Scotland), and practice list size (≤5700, >5700) as fixed effects, and GP practice as a random effect.

N refers to number of participants with data available at 24 months for each outcome. ICC: Intraclass Correlation Coefficient.

(a) Number (%) of participants prescribed 0, 1, or 2+ oral antidiabetic medications at 12 months were: Intervention – 109 (73·6%), 26 (17·6%), 13 (8·8%); Control – 27 (18·2%), 70 (47·3%), 51 (34·5%).

(b) Log-transformed values were used in the regression analysis.

(c) Number with data a 2 year follow-up

Table 2: Serious Adverse Events up to 24 months follow-up

		All	Control	Intervention
Number of Participants		306	149	157
Number of SAEs		40	25	15
Number (%) of participants with any SAE		30 (9·8%)	19 (12·8%)	11 (7·0%)
Number (%) of participants with any SAEs,classified by MedDRA System Organ Class (SOC) and Preferred Term (PT):				
SOC:	CARDIAC DISORDERS	4 (1·3%)	1 (0·7%)	3 (1·9%)
PT:	Acute myocardial infarction	1 (0.3%)	0 (0.0%)	1 (0.6%)
	Angina pectoris	1 (0·3%)	0 (0·0%)	1 (0·6%)
	Atrial fibrillation	1 (0·3%)	1 (0·7%)	0 (0·0%)
	Coronary artery disease	1 (0.3%)	0 (0.0%)	1 (0.6%)
SOC:	GASTROINTESTINAL DISORDERS	4 (1·3%)	1 (0·7%)	3 (1·9%)
PT:	Abdominal pain	1 (0·3%)	0 (0·0%)	1 (0·6%)
	Abdominal strangulated hernia	1 (0·3%)	0 (0·0%)	1 (0·6%)
	Diverticulum	1 (0·3%)	0 (0·0%)	1 (0·6%)
	Gastric disorder	1 (0·3%)	1 (0·7%)	0 (0·0%)
SOC:	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0·3%)	1 (0·7%)	0 (0·0%)
PT:	Sudden death	1 (0·3%)	1 (0·7%)	0 (0·0%)
SOC:	HEPATOBILIARY DISORDERS	2 (0·7%)	1 (0·7%)	1 (0·6%)
PT:	Cholelithiasis	1 (0·3%)	0 (0·0%)	1 (0·6%)
	Non-alcoholic steatohepatitis	1 (0·3%)	1 (0·7%)	0 (0·0%)
SOC:	INFECTIONS AND INFESTATIONS	5 (1·6%)	3 (2·0%)	2 (1·3%)
PT:	Arthritis bacterial	1 (0·3%)	1 (0·7%)	0 (0·0%)
	Diverticulitis	2 (0·7%)	1 (0·7%)	1 (0·6%)
	Urinary tract infection	1 (0·3%)	0 (0·0%)	1 (0·6%)
	Wound infection	1 (0.3%)	1 (0.7%)	0 (0.0%)
SOC:	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (1·0%)	1 (0·7%)	2 (1·3%)

		All	Control	Intervention
PT:	Humerus fracture	1 (0·3%)	1 (0·7%)	0 (0·0%)
	Incisional hernia	1 (0·3%)	0 (0·0%)	1 (0·6%)
	Synovial rupture	1 (0·3%)	0 (0·0%)	1 (0·6%)
SOC:	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0·3%)	1 (0·7%)	0 (0·0%)
PT:	Back pain	1 (0·3%)	1 (0·7%)	0 (0·0%)
SOC:	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	5 (1·6%)	5 (3·4%)	0 (0·0%)
PT:	Bladder cancer	1 (0·3%)	1 (0·7%)	0 (0·0%)
	Colon cancer	2 (0·7%)	2 (1·3%)	0 (0·0%)
	Prostate cancer	1 (0·3%)	1 (0·7%)	0 (0·0%)
	Renal cell carcinoma	1 (0·3%)	1 (0·7%)	0 (0·0%)
SOC:	NERVOUS SYSTEM DISORDERS	6 (2.0%)	4 (2.7%)	2 (1.3%)
PT:	Cerebellar infarction	1 (0.3%)	1 (0.7%)	0 (0.0%)
	Cerebrovascular accident	1 (0.3%)	1 (0.7%)	0 (0.0%)
	Dizziness	1 (0.3%)	0 (0.0%)	1 (0.6%)
	Guillain-Barre syndrome	1 (0.3%)	1 (0.7%)	0 (0.0%)
	Presyncope	1 (0.3%)	0 (0.0%)	1 (0.6%)
	Sciatica	1 (0.3%)	0 (0.0%)	1 (0.6%)
	VIIth nerve paralysis	1 (0.3%)	1 (0.7%)	0 (0.0%)
SOC:	PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (0.3%)	0 (0.0%)	1 (0.6%)
PT:	HELLP syndrome	1 (0.3%)	0 (0.0%)	1 (0.6%)
SOC:	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (1.3%)	4 (2.7%)	0 (0.0%)
PT:	Asthma	2 (0.7%)	2 (1.3%)	0 (0.0%)
	Dyspnoea	2 (0.7%)	2 (1.3%)	0 (0.0%)
SOC:	SURGICAL AND MEDICAL PROCEDURES	1 (0.3%)	1 (0.7%)	0 (0.0%)
PT:	Toe amputation	1 (0.3%)	1 (0.7%)	0 (0.0%)
SOC:	VASCULAR DISORDERS	1 (0.3%)	1 (0.7%)	0 (0.0%)
PT:	Aortic aneurysm rupture	1 (0.3%)	1 (0.7%)	0 (0.0%)

Table S1: Baseline characteristics by attendance of 2-year follow-up visit. ITT population. P-values have been derived using Wilcoxon tests or Exact Fisher tests, as appropriate.

	All	Did not attend	Did attend	p-value
	N = 298	N = 41	N = 257	
Age (years)				
Number	298	41	257	
Mean (SD)	54.4 (7.6)	49.2 (8.8)	55.2 (7.0)	
Median	55.1	48.9	55.6	p<0.0001 [W]
(Q1, Q3)	(49.2, 60.9)	(43.8, 54.3)	(50.6, 61.1)	
[Min, Max]	[30.8, 65.9]	[30.8, 65.4]	[32.4, 65.9]	
Sex				
Number	298	41	257	
N (%) Male	176 (59.1%)	21 (51.2%)	155 (60.3%)	p=0.3064 [F]
N (%) Female	122 (40.9%)	20 (48.8%)	102 (39.7%)	
Years since diabetes diagnosis				
Number	298	41	257	
Mean (SD)	3.0 (1.7)	2.1 (1.8)	3.1 (1.7)	
Median	3.0	1.6	3.1	p=0.0001 [W]
(Q1, Q3)	(1.5, 4.5)	(0.6, 3.5)	(1.7, 4.6)	
[Min, Max]	[0.0, 6.0]	[0.1, 5.8]	[0.0, 6.0]	
HbA1c (mmol/mol), from GP records				
Number	298	41	257	
Mean (SD)	61.6 (13.9)	66.1 (16.8)	60.9 (13.3)	
Median	58.0	62.0	57.0	p=0.0748 [W]
(Q1, Q3)	(51.0, 68.0)	(52.0, 79.0)	(51.0, 67.0)	
[Min, Max]	[43.0, 107.0]	[44.0, 105.0]	[43.0, 107.0]	
HbA1c (%), from GP records				

Table S1: Baseline characteristics by attendance of 2-year follow-up visit. ITT population. P-values have been derived using Wilcoxon tests or Exact Fisher tests, as appropriate.

	All	Did not attend	Did attend	p-value
	N = 298	N = 41	N = 257	
Number	298	41	257	
Mean (SD)	7.79 (1.27)	8.20 (1.54)	7.72 (1.21)	
Median	7.46	7.82	7.37	p=0.0748 W
(Q1, Q3)	(6.82, 8.37)	(6.91, 9.38)	(6.82, 8.28)	
[Min, Max]	[6.09, 11.94]	[6.18, 11.76]	[6.09, 11.94]	
Weight (kg)				
Number	298 (0)	41 (0)	257 (0)	
Mean (SD)	99.9 (16.4)	101.7 (17.8)	99.6 (16.2)	
Median	99.0	102.0	98.7	p=0.5234 W
(Q1, Q3)	(87.7, 109.5)	(88.9, 109.7)	(87.6, 109.0)	
[Min, Max]	[67.0, 149.1]	[74.3, 146.7]	[67.0, 149.1]	
BMI (kg/m^2)				
Number	298 (0)	41 (0)	257 (0)	
Mean (SD)	34.6 (4.4)	35.4 (4.4)	34.5 (4.4)	
Median	34.1	35.9	34.0	p=0.1813 W
(Q1, Q3)	(31.1, 37.5)	(32.9, 38.4)	(30.8, 37.4)	
[Min, Max]	[27.3, 44.9]	[27.8, 44.9]	[27.3, 44.9]	
SBP (mmHg)				
Number	298 (0)	41 (0)	257 (0)	
Mean (SD)	134.9 (16.9)	129.8 (17.9)	135.8 (16.6)	
Median	134.0	128.0	135.0	p=0.0268 W
(Q1, Q3)	(122.1, 144.0)	(119.0, 138.0)	(123.0, 145.0)	
[Min, Max]	[100.0, 194.5]	[100.0, 171.5]	[100.0, 194.5]	
History of Heart Failure				
Number	298	41	257	
N (%) Yes	2 (0.7%)	2 (4.9%)	0 (0.0%)	p=0.0185 F
N (%) No	296 (99.3%)	39 (95.1%)	257 (100.0%)	
Albumin/Creatinine Ratio (mg/mmol) (values <0.5 imputed as 0.25)				

Table S1: Baseline characteristics by attendance of 2-year follow-up visit. ITT population. P-values have been derived using Wilcoxon tests or Exact Fisher tests, as appropriate.

	All	Did not attend	Did attend	p-value
	N = 298	N = 41	N = 257	
Nobs (Nmiss)	292 (6)	37 (4)	255 (2)	
Mean (SD)	2.16 (6.89)	5.40 (15.37)	1.69 (4.38)	
Median	0.25	0.84	0.25	p=0.0050 W
(Q1, Q3)	(0.25, 1.38)	(0.25, 3.44)	(0.25, 1.20)	
[Min, Max]	[0.25, 89.97]	[0.25, 89.97]	[0.25, 46.85]	
Microalbuminuria, defined as ACR≥3.5 (female) or ACR≥2.5 (male)				
Nobs (Nmiss)	292 (6)	37 (4)	255 (2)	
N (%) No	253 (86.6%)	26 (70.3%)	227 (89.0%)	p=0.0040 F
N (%) Yes	39 (13.4%)	11 (29.7%)	28 (11.0%)	
C-rP (mg/l)				
Nobs (Nmiss)	291 (7)	37 (4)	254 (3)	
Mean (SD)	3.33 (3.64)	4.45 (4.25)	3.17 (3.52)	
Median	2.21	3.29	2.04	p=0.0025 W
(Q1, Q3)	(1.12, 4.32)	(1.95, 5.26)	(1.10, 3.86)	
[Min, Max]	[0.10, 32.09]	[0.51, 24.70]	[0.10, 32.09]	
HDL Cholesterol (mmol/l)				
Nobs (Nmiss)	291 (7)	37 (4)	254 (3)	
Mean (SD)	1.12 (0.28)	1.02 (0.26)	1.13 (0.28)	
Median	1.09	0.98	1.11	p=0.0149 W
(Q1, Q3)	(0.92, 1.28)	(0.88, 1.15)	(0.94, 1.30)	
[Min, Max]	[0.35, 2.61]	[0.35, 1.72]	[0.40, 2.61]	

Table S2 Summary of weight change from baseline by use of antidiabetic medications

			Weight change at	
			12 Months	24 Months
All participants			-5.3 (7.6), n=285	-4.8 (6.4), n=272
On anti-diabetic medication at				
Baseline	12 Months	24 Months		
No	No	No	-7.9 (7.1), n=45	-5.3 (5.2), n=44
No	No	Yes	-2.8 (5.3), n=7	-2.8 (4.3), n=8
No	Yes	No	-5.3 (-), n=1	-3.7 (-), n=1
No	Yes	Yes	-4.2 (5.6), n=7	-6.0 (3.9), n=7
Yes	No	No	-13.4 (8.3), n=52	-9.9 (7.5), n=53
Yes	No	Yes	-5.3 (6.7), n=14	-4.4 (2.7), n=16
Yes	Yes	No	1.9 (5.2), n=2	3.3 (7.1), n=2
Yes	Yes	Yes	-1.8 (5.0), n=140	-3.0 (5.7), n=140

Table S3 Summary of weight change from baseline by use of anti-diabetic medications

			Weight change at	
			12 Months	24 Months
All			-5.3 (7.6), n=285	-4.8 (6.4), n=272
On anti-diabetic medication at				
Baseline	12 Months	24 Months		
Intervention group				
No	No	No	-11.7 (6.8), n=26	-7.8 (5.1), n=26
No	No	Yes	-3.7 (7.7), n=2	-4.2 (6.5), n=3
No	Yes	No	- (-), n=0	- (-), n=0
No	Yes	Yes	- (-), n=0	- (-), n=0
Yes	No	No	-13.7 (8.1), n=51	-10.1 (7.5), n=52
Yes	No	Yes	-5.3 (6.7), n=14	-4.4 (2.7), n=16
Yes	Yes	No	- (-), n=0	- (-), n=0
Yes	Yes	Yes	-6.4 (6.6), n=32	-5.5 (5.6), n=32
Control group				
No	No	No	-2.7 (3.2), n=19	-1.6 (2.4), n=18
No	No	Yes	-2.5 (5.2), n=5	-2.0 (2.8), n=5
No	Yes	No	-5.3 (-), n=1	-3.7 (-), n=1
No	Yes	Yes	-4.2 (5.6), n=7	-6.0 (3.9), n=7
Yes	No	No	-0.4 (-), n=1	-2.1 (-), n=1
Yes	No	Yes	- (-), n=0	- (-), n=0
Yes	Yes	No	1.9 (5.2), n=2	3.3 (7.1), n=2
Yes	Yes	Yes	-0.5 (3.4), n=108	-2.3 (5.6), n=108