Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

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Summary

Background Type 2 diabetes is a chronic disorder that requires lifelong treatment. We aimed to assess whether intensive weight management within routine primary care would achieve remission of type 2 diabetes.

Methods We did this open-label, cluster-randomised trial (DiRECT) at 49 primary care practices in Scotland and the Tyneside region of England. Practices were randomly assigned (1:1), via a computer-generated list, to provide either a weight management programme (intervention) or best-practice care by guidelines (control), with stratification for study site (Tyneside or Scotland) and practice list size (>5700 or ≤5700). Participants, carers, and research assistants who collected outcome data were aware of group allocation; however, allocation was concealed from the study statistician. We recruited individuals aged 20–65 years who had been diagnosed with type 2 diabetes within the past 6 years, had a body-mass index of 27–45 kg/m², and were not receiving insulin. The intervention comprised withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance. Co-primary outcomes were weight loss of 15 kg or more, and remission of diabetes, defined as glycated haemoglobin (HbA_{1c}) of less than 6·5% (<48 mmol/mol) after at least 2 months off all antidiabetic medications, from baseline to 12 months. These outcomes were analysed hierarchically. This trial is registered with the ISRCTN registry, number 03267836.

Findings Between July 25, 2014, and Aug 5, 2017, we recruited 306 individuals from 49 intervention (n=23) and control (n=26) general practices; 149 participants per group comprised the intention-to-treat population. At 12 months, we recorded weight loss of 15 kg or more in 36 (24%) participants in the intervention group and no participants in the control group (p<0·0001). Diabetes remission was achieved in 68 (46%) participants in the intervention group and six (4%) participants in the control group (odds ratio 19·7, 95% CI 7·8–49·8; p<0·0001). Remission varied with weight loss in the whole study population, with achievement in none of 76 participants who gained weight, six (7%) of 89 participants who maintained 0–5 kg weight loss, 19 (34%) of 56 participants with 5–10 kg loss, 16 (57%) of 28 participants with 10–15 kg loss, and 31 (86%) of 36 participants who lost 15 kg or more. Mean bodyweight fell by 10·0 kg (SD 8·0) in the intervention group and 1·0 kg (3·7) in the control group (adjusted difference –8·8 kg, 95% CI –10·3 to –7·3; p<0·0001). Quality of life, as measured by the EuroQol 5 Dimensions visual analogue scale, improved by 7·2 points (SD 21·3) in the intervention group, and decreased by 2·9 points (15·5) in the control group (adjusted difference 6·4 points, 95% CI 2·5–10·3; p=0·0012). Nine serious adverse events were reported by seven (4%) of 157 participants in the intervention group and two were reported by two (1%) participants in the control group. Two serious adverse events (biliary colic and abdominal pain), occurring in the same participant, were deemed potentially related to the intervention. No serious adverse events led to withdrawal from the study.

Interpretation Our findings show that, at 12 months, almost half of participants achieved remission to a non-diabetic state and off antidiabetic drugs. Remission of type 2 diabetes is a practical target for primary care.

Funding Diabetes UK.

Published **Online** December 5, 2017 http://dx.doi.org/10.1016/S0140-6736(17)33102-1

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(17)33100-8

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Introduction

Type 2 diabetes affects almost one in ten adults in the UK, and 422 million adults worldwide.[1,2] Most people with type 2 diabetes have disease-related morbidity and reduced longevity. The disease is particularly devastating for the growing numbers of younger people affected, who tend to be more obese and lose more life-years through diabetes.[3] Current guidelines for management of type 2 diabetes focus heavily on multiple drug treatments to reduce blood glucose and the associated elevated risks of cardiovascular disease, but life expectancy remains substantially reduced.

Type 2 diabetes is strongly related to weight gain in adult life and accumulation of excess fat within the liver and pancreas. The twin cycle hypothesis,[4] which postulated that type 2 diabetes is caused specifically by excess fat within the liver and pancreas, was tested by inducing negative energy balance with a 600–700 kcal/day diet. Liver insulin resistance and fat content normalised within 7 days, with first-phase insulin response and pancreas fat content normalising over 8 weeks.[5] In a subsequent parallel-group study,[6] the underlying changes were shown to remain stable over a 6 month period of isocaloric eating.

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Research in context

Evidence before this study

Between Jan 1, 1980, and Oct 30, 2017, we searched clinical guidelines and published reports for non-surgical clinical trials with a primary outcome of remission of type 2 diabetes. Our search terms were "diabetes and remission" and "clinical trial", and we restricted the search to English-language publications only. No trials were identified. Evidence-based clinical guidelines for type 2 diabetes focus on pharmacological treatments to reduce blood glucose and glycated haemoglobin (HbA_{1c}). Diet and lifestyle are mentioned as part of efforts to control glycaemia levels, but diabetes remission by this route is rarely discussed. Weight gain, however, is a dominant causal factor behind type 2 diabetes in susceptible individuals. Although bariatric surgery can achieve remission of diabetes in about 75% of people with type 2 diabetes, only a small proportion could or would wish to undergo surgical treatments.

Added value of this study

Our DiRECT study provides the first evidence from a randomised trial of a dietary and lifestyle intervention with remission of type 2 diabetes as a primary outcome. The findings show that more than a quarter of people with type 2 diabetes of up to 6 years' duration are interested in using a practical weight management programme delivered by existing staff in primary care (including a high proportion of men), and that almost half of those undertaking the intervention can achieve and maintain remission at 12 months. Achieved weight reductions were around 10 kg on average in the intervention group.

Implications of all the available evidence

DiRECT is a pragmatic trial done under real-life, primary care conditions in a sample of people with type 2 diabetes typical of those managed routinely in this setting. Relatively low-intensity training and support of existing staff, and appropriate resource redistribution, could facilitate provision of this intervention and dissemination of the results widely across health services. This approach would offer the chance to achieve remission of type 2 diabetes and its associated benefits, including improved quality of life. The potential personal and health-service-related benefits are considerable.

These pathophysiological studies established how and why people with type 2 diabetes can be returned to normal glucose control by calorie restriction. The challenge remained to test whether such an intervention was practicable in routine primary care. Other studies involving weight loss of at least 10–15 kg have been shown to achieve normalisations of blood glucose in people with short-duration type 2 diabetes,[7–10] but no previous trial based on dietary change has assessed sustained (ie, ≥1 year) disease remission as a primary outcome.

We did the Diabetes Remission Clinical Trial (DiRECT) to assess whether effective weight management, delivered in the primary care setting, could produce sustained remission of type 2 diabetes.

Methods

Study design and participants

We did this open-label, cluster-randomised trial at 49 primary care practices in Scotland and the Tyneside region of England. General practices (GPs) representing populations with a wide range of social and geographic features were invited to participate by the Primary Care Research Network (PCRN) in Scotland, and North East Commissioning Support in Tyneside. Ethics approval was granted by West 3 Ethics Committee in January, 2014, with approvals by the National Health Service (NHS) health board areas in Scotland and clinical commissioning groups in Tyneside. The protocol, including details of recruitment methods, study conduct, and planned analyses, has been published elsewhere.[11]

There were no specific eligibility criteria for practices. Eligible participants were aged 20–65 years, had been diagnosed with type 2 diabetes within the previous 6 years, and had a body-mass index (BMI) of 27–45 kg/m². Exclusion criteria were current insulin use, a glycated haemoglobin (HbA_{1c}) concentration of 12% or more (≥108 mmol/mol), weight loss of more than 5 kg within the past 6 months, a recent on-record estimated glomerular filtration rate of less than 30 mL/min per 1·732 m², severe or unstable heart failure, participation in another clinical research trial, substance abuse, known cancer, myocardial infarction within the previous 6 months, learning difficulties, current treatment with anti-obesity drugs, presence of an eating disorder or purging behaviour, pregnancy or consideration of pregnancy, and hospital admission for depression or use of antipsychotic drugs. After review of data from the first practices to enter the study, it was necessary to tighten the criteria for diagnosis of type 2 diabetes to exclude patients who had already achieved non-diabetic HbA_{1c}. The inclusion criteria were revised to specify that the most recent HbA_{1c} value should be greater than 6·0% (>43 mmol/mol) and, if less than 6·5% (<48 mmol/mol), individuals should still be receiving antidiabetic medication. This substantial amendment was approved by the trial steering committee, ethics committee, and all NHS research and development departments on Nov 27, 2014. All participants provided written informed consent.

Randomisation and masking

The primary care practice was the unit of randomisation to enable consistent management of type 2 diabetes within practices and avoid contamination between treatment groups. Practices agreeing to participate were

randomly assigned (1:1) by the Robertson Centre for Biostatistics (University of Glasgow, UK), via a computer-generated list, to provide either an evidence-based weight management programme (Counterweight-Plus; intervention)[12] or best-practice care by guidelines (control). Randomisation was stratified to maintain balance for practice list size (>5700 or ≤5700) across intervention groups within each study region.

Due to the nature of the lifestyle intervention being examined, participants, carers, and research assistants who collected outcome data were aware of group allocation; however, allocation was concealed from the study statistician in charge of developing and conducting the statistical analysis programme (AM).

Procedures

Potentially eligible participants were mailed an invitation pack, including an information sheet, by the PCRN (Scotland) and GP staff in Tyneside (independently of the research team), and asked to respond using a reply-paid envelope. To help balance the incentive of the intervention itself, participants in the control group were offered a £50 Amazon voucher. Individuals who did not respond were sent a reminder or telephoned; those interested in participating were invited to an initial appointment.

A nurse or dietitian (as available locally) in each intervention practice was given a total of 8 h structured training by the study research dietitians experienced in Counterweight-Plus. Training followed a standard protocol, to minimise variability and maintain fidelity across all practices. Mentoring of nurses and dietitians was done by the study research dietitians during each stage of the intervention, with feedback as required.

Participants in the intervention group were asked to follow the Counterweight-Plus weight management programme,[12] with a stated aim of achieving and maintaining at least 15 kg weight loss for the maximum number of participants and an emphasis on flexibility to accommodate individual circumstances and optimise outcomes. Weight loss was induced with a total diet replacement phase using a low energy formula diet (825–853 kcal/day; 59% carbohydrate, 13% fat, 26% protein, 2% fibre) for 3 months (extendable up to 5 months if wished by participant), followed by structured food reintroduction of 2–8 weeks (about 50% carbohydrate, 35% total fat, and 15% protein), and an ongoing structured programme with monthly visits for long-term weight loss maintenance. All oral antidiabetic and antihypertensive drugs were discontinued on day 1 of the weight management programme, with standard protocols for drug reintroduction under national clinical guidelines, if indicated by regular monitoring of blood glucose and blood pressure.[11] Antihypertensive drugs were withdrawn because blood pressure rapidly decreases upon commencement of a low energy diet.[6]

Participants were encouraged to maintain their usual physical activities during total diet replacement, but not asked to increase activity at this stage. Step counters were provided at the start of food reintroduction, and physical activity strategies were introduced, to help participants in the intervention group to reach and maintain their individual sustainable maximum—up to 15 000 steps per day. Physical activity and sleep were objectively measured over 7 days by use of wrist-worn triaxial accelerometers; data were assessed with validated calibration and analysis algorithms.[13,14]

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[15] and the Scottish Intercollegiate Guidelines Network in Scotland.[16] 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) after at least 2 months off all antidiabetic medications, from baseline to month 12. Secondary outcomes assessed at 12 months were quality of life, as measured by the EuroQol 5 Dimensions (EQ-5D); serum lipids; and physical activity. Other presepcified outcomes included programme acceptability, sleep quality, and blood pressure, as detailed in the protocol.[11] We additionally assessed exploratory outcomes of effects on changes in medications.

All outcome data were collected at baseline and at 12 months. For participants who ceased to engage and did not attend their 12 month trial appointment, data from GP records (within a window of plus or minus 3 months of the scheduled follow-up date) were used if available, as prespecified in the protocol.[11]

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 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. To provide comparability with other published data for weight changes, we did a sensitivity analysis with different models to impute values for 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 1 year (the effect size deemed potentially important, a priori) compared with an estimated 5% in the control group, enrolment of ten participants per

	Intervention group (n=149)	Control group (n=149)
Sex		
Female	66 (44%)	56 (38%)
Male	83 (56%)	93 (62%)
White ethnicity	146 (98%)	147 (99%)
Age (years)	52·9 (7·6)	55·9 (7·3)
Weight (kg)	101·0 (16·7)	98·8 (16·1)
Body-mass index (kg/m²)	35·1 (4·5)	34·2 (4·3)
Waist (cm)	107·5 (8·4)	106·5 (8·9)
Systolic blood pressure (mm Hg)	132·7 (17·5)	137·2 (16·0)
Diastolic blood pressure (mm Hg)	84·6 (10·2)	85·5 (8·8)
Time since diabetes diagnosis (years)		
Mean (SD)	3·0 (1·7)	3·0 (1·8)
Median (range)	3·1 (0·0–6·0)	2·6 (0·2–6·0)
HbA_{1c}		
%	7·7 (1·25)	7·5 (1·05)
mmol/mol	60 (13·7)	58 (11·5)
Fasting glucose (mmol/L)	9·22 (3·29)	8·82 (2·54)
Prescribed oral antidiabetic medication	111 (74·5)	115 (77·2)
Number of oral antidiabetic medications		
0	38 (26%)	34 (23%)
1	65 (44%)	79 (53%)
≥2	46 (31%)	36 (24%)
Hypertension	81 (54%)	88 (59·1)
Any cardiovascular disease	13 (9%)	24 (16%)
Prescribed statins	93 (62%)	100 (67%)
Albumin-to-creatinine ratio (mg/mmol)*	3·16 (9·4)	1·19 (2·4)
Microalbuminuria†	28 (19%)	11 (7%)
Estimated glomerular filtration rate (mL/min per 1·73 m²)	101·5 (23·9)	95·8 (25·2)
<60	3 (2%)	6 (4%)
Total cholesterol (mmol/L)	4·34 (1·1)	4·31 (1·2)
HDL cholesterol (mmol/L)	1·08 (0·25)	1·16 (0·31)
Triglycerides (mmol/L)	1·83 (1·4–2·4)	1·66 (1·3–2·5)
Retinopathy	14 (9%)	21 (14%)
Neuropathy	2 (1%)	2 (1%)
Microvascular complications	19 (13%)	26 (18%)

Data are n (%), mean (SD), or median (IQR), unless otherwise specified. HbA_{1c}=glycated haemoglobin. *Values less than 0·5 mg/mmol were imputed as 0·25 mg/mmol. †Defined as an albumin-to-creatinine ratio of 3·5 mg/mmol or more for women and 2·5 mg/mmol or more for men.

Table 1: **Baseline characteristics**

practice (fixed), an intraclass 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. For serum triglyceride, groups were compared with a linear regression model of log-transformed values, with adjustment for baseline log triglyceride. All models were adjusted for the minimisation variables (study centre and practice list size). Models of continuous outcomes were also adjusted for the baseline measurement of the outcome.

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–Mann–Whitney tests, using both the 12 month value of the outcome measure 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. This trial is registered with the ISRCTN registry, number 03267836.

Role of the funding source

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

Results

Recruitment and baseline data have been published elsewhere.[17] Between July 25, 2014, and Aug 5, 2016, we recruited 306 individuals from 49 intervention (n=23) and control (n=26) practices; 149 participants per group comprised the intention-to-treat population (figure 1). Baseline characteristics were similar between groups (table 1).[17]

23 (8%) participants were lost to follow-up at 12 months, with 128 (86%) participants in the intervention group and 147 (99%) participants in the control group attending the 12 month study assessment. Four (3%) participants in the intervention group did not provide a 12 month blood sample for HbA_{1c} measurement. Additional data were obtained from GP records for weight for ten (3%) participants (n=9 intervention and n=1 control) and HbA_{1c} for 15 (5%) participants (n=14 and n=1, respectively). GP records were unavailable for one participant in each group. Thus, data for the first primary outcome (weight loss ≥15kg) were available for 285 (96%) participants (n=137 intervention and n=148 control), and for the second primary outcome (diabetes remission) for 290 (97%) participants (n=142 and n=148, respectively). For the intention-to-treat analysis, the remaining participants with missing data were assumed to have not met each primary outcome (figure 1).

In the intervention group, six (4%) participants consented, but thereafter never engaged with the intervention, and 26 (17%) participants withdrew from treatment during the first 12 months (n=15 during total diet replacement, n=6 during stepped food reintroduction,

and n=5 during weight loss maintenance). The intention-to-treat analysis included data for all these participants.

At 12 months, we recorded weight loss of 15 kg or more in 36 (24%) participants in the intervention group and no participants in the control group (Fisher's exact p<0·0001; figure 2). We recorded diabetes remission in 68 (46%) participants in the intervention group and six (4%) participants in the control group (odds ratio 19·7, 95% CI 7·8–49·8; p<0·0001; figure 2).

Mean bodyweight fell by 10·0 kg in the intervention group and by 1·0 kg in the control group (adjusted difference at –8·8 kg, 95% CI –10·3 to –7·3; p<0·0001; table 2). Similar patterns were recorded for BMI and weight change as a percentage of baseline weight (appendix p 2). Sensitivity analyses using alternative assumptions regarding missing data for weight at 12 months gave similar results (appendix pp 2, 3). For participants in the intervention group who engaged with the intervention, weight fell sharply during the total diet replacement phase, by 14·5 kg (95% CI 13·4–15·5), followed by small increases during the food reintroduction phase (1·0 kg [0·3–1·6]) and the weight loss management phase (1·9 kg [1·2–2·5]; figure 3). Patients who completed the total diet replacement phase had greater weight loss, and those who completed the food reintroduction phase less weight gain, than did patients who started, but did not complete, each phase (figure 3, appendix p 4).

Mean HbA_{1c} fell by –0·9% (SD 1·4) in the intervention group and increased by 0·1% (1·1) in the control group (adjusted difference –0·85%, 95% CI –1·10 to –0·59; p<0·0001; table 2). For all 298 participants, diabetes remission was achieved by no participant who did not lose weight at 12 months, six (7%) of 89 participants who maintained 0–5 kg weight loss, 19 (34%) of 56 participants with 5–10 kg loss, 16 (57%) of 28 participants with 10–15 kg loss, and 31 (86%) of 36 participants who lost 15 kg or more (figure 2, appendix pp 11). For the six participants who achieved remission in the control group, mean weight loss was 4·5 kg (SD 2·8; min–max range 1·1–8·4), falling from 104·9 kg (SD 21·4) at baseline to 100·3 kg (20·2) at 12 months.

At baseline, the proportion of participants taking no, one, or two or more antidiabetic medications was similar between groups (table 1). At 12 months, 109 (74%) of 148 participants in the intervention group were taking no antidiabetic medications (mean HbA_{1c} 6·4% [46·8 mmol/mol]) compared with 27 (18%) of 148 participants in the control group (mean HbA_{1c} 7·2% [54·6 mmol/mol]; p=0·0032; appendix pp 5, 12, 13). The mean number of antidiabetic medications prescribed decreased in the intervention group and increased in the control group (table 2). In the control group, antidiabetic medications were commenced in eight (5%) participants and stopped in one (1%) participant who lost no weight and had a HbA_{1c} value of 7·9% (63 mmol/mol) at 12 months.

For quality of life, the EQ-5D visual analogue scale improved by 7·2 points (SD 21·3) in the intervention group, and decreased by 2·9 points (15·5) in the control group (adjusted difference 6·4 points, 95% CI 2·5–10·3; p=0·0012; table 2, appendix p 2).

Mean serum triglyceride decreased by 0·31 mmol/L (SD 1·33) in the intervention group, and increased by 0·09 mmol/L (0·92) in the control group (appendix p 9). At 12 months, triglycerides were 20% (95% CI 11–28) lower

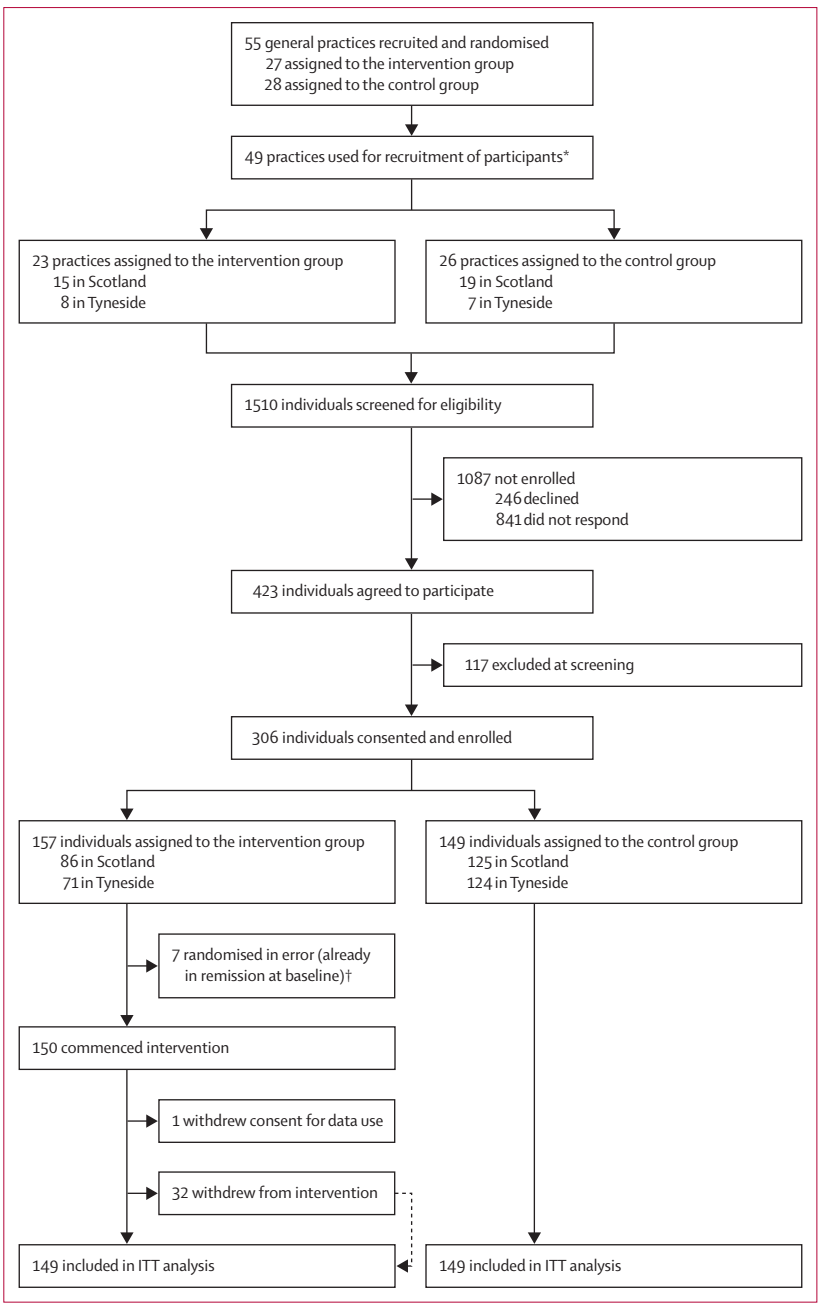

Figure 1: **Trial profile**
ITT=intention-to-treat. *Four intervention practices and two control practices were not required for recruitment, which was done sequentially by practice to allow for training of practice staff. Therefore, 49 practices were asked to recruit participants. †Baseline glycated haemoglobin less than 6·5% (<48 mmol/mol) without antidiabetic medication.

See **Online** for appendix

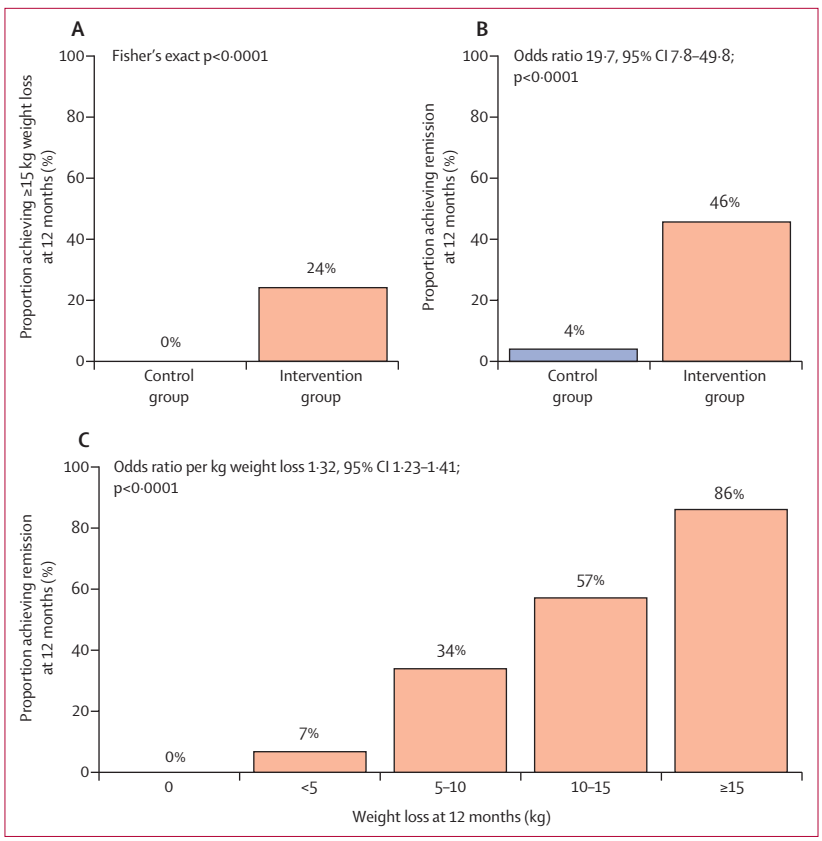

Figure 2: **Primary outcomes and remission of diabetes in relation to weight loss at 12 months**
(A) First co-primary outcome: achievement of at least 15 kg weight loss at 12 months. (B) Second co-primary outcome: remission of diabetes (glycated haemoglobin <6·5% [48mmol/mol], off antidiabetic medication for 2 months). (C) Remission of diabetes, in relation to weight loss achieved at 12 months (both groups combined).

in the intervention group than in the control group (p<0·0001). Changes in concentrations of total or HDL cholesterol did not differ significantly between groups (appendix p 9). There were no differences between groups in change in levels of measured physical activity over 12 months (appendix p 6).

Programme acceptability was assessed in several ways. Full process evaluation and analysis of qualitative information from transcribed interviews of participants and health-care staff, during each phase of the intervention, will be presented separately. Figure 3 shows retention and attrition rates at each phase of the intervention, and adherence reflected by weight changes.

Overall, 32 (21%) participants withdrew prematurely from the intervention programme. For participants who commenced treatment (n=26), the main reason for withdrawal was a social reason (appendix p 7). In assessment of sleep quality, changes in neither sleep duration nor sleep efficiency differed significantly between groups at 12 months (appendix p 6).

Mean blood pressure at 12 months was similar between groups (table 2). However, antihypertensive drugs had been withdrawn in 38 (48%) of 80 participants who had taken them at baseline in the intervention group, and in no participants in the control group. At 12 months, antihypertensive drugs were being prescribed to 47 (32%) of 148 participants in the intervention group (n=29 one drug, n=18 two or more drugs), compared with 91 (61%) of 148 participants in the control group (n=43 one drug, n=48 two or more drugs; p=0·0001; appendix p 8).

At 12 months, the number of participants being prescribed medications other than antidiabetic and antihypertensive was lower in the intervention group than the control group (n=121 [82%] *vs* n=133 [90%]; p=0·0486), but there was no difference in the number of other medications prescribed (median 3 [IQR 1–5] in both groups) or in the change from baseline (0 [–1 to 1] in the intervention group *vs* 0 [0–1] in the control group; p=0·6920).

Mean drug prescriptions (including antidiabetic, antihypertensive, lipid-lowering, and all other medications) at baseline were 5·6 (SD 3·5) in the intervention group and 5·7 (3·8) in the control group; at 12 months, these figures were 4·8 (4·3) and 6·5 (4·1), respectively (p<0·0001). Antidepressant drugs were being taken by 40 (27%) participants in the intervention group and 28 (19%) participants in the control group at baseline; no significant change was observed at 12 months (n=40 [27%] *vs* n=31 [21]; p=0·2506; appendix). In the intervention group, the proportion of participants taking no prescription drugs increased from 2% (n=3) at baseline to 11·5% (n=17) at 12 months, with no change in the control group (n=3 [2%] at both timepoints; Fisher's exact p=0·0018).

During the 12 month follow-up period, nine serious adverse events were reported by seven (4%) of 157 participants in the intervention group and two were reported by two (1%) participants in the control group (table 3). No participants died. Two serious adverse events (biliary colic and abdominal pain), occurring in the same participant, were deemed potentially related to the intervention. The remainder of events were for brief overnight admissions for unrelated events or investigations. No serious adverse events led to withdrawal from the study.

The appendix (p 10) shows the number of participants who self-reported adverse events that were prespecified as being of interest during the intervention. Of 139 participants who underwent total diet replacement, the most frequently reported adverse events, occurring over a mean duration of 16·0 weeks (SD 5·3), were constipation (n=65), increased sensitivity to cold (n=51), headache (n=53), and dizziness (n=49). Most of these adverse events were of mild or moderate severity and dissipated over time (appendix p 10). Besides constipation, no event required treatment. Fewer adverse events were reported during the food reintroduction and weight loss management phases than during the total diet replacement phase (appendix p 10). Information about symptoms was collected only from participants in the intervention group.

	n*	Mean (SD)			Intervention effect		ICC
		Baseline	12 months	Change	Estimate (95% CI)	p value	
Weight (kg)	..	..	..	..	−8·8 (−10·3 to −7·3)	<0·0001	<0·01
Intervention	137	100·4 (16·5)	90·4 (16·4)	−10·0 (8·0)	..	..	..
Control	148	98·7 (16·1)	97·7 (16·4)	−1·0 (3·7)	..	..	..
HbA_{1c} (mmol/mol)	..	..	..	..	−9·3 (−12·1 to −6·5)	<0·0001	<0·01
Intervention	138	60·2 (12·7)	50·6 (13·3)	−9·6 (15·4)	..	..	..
Control	148	58·2 (11·6)	59·6 (12·1)	1·4 (11·6)	..	..	..
HbA_{1c} (%)	..	..	..	..	−0·85 (−1·10 to −0·59)	<0·0001	<0·01
Intervention	138	7·7 (1·2)	6·8 (1·2)	−0·9 (1·4)	..	..	..
Control	148	7·5 (1·1)	7·6 (1·1)	0·1 (1·1)	..	..	
Number of prescribed oral antidiabetic medications†	..	..	..	..	−0·97 (−1·11 to −0·84)	<0·0001	<0·01
Intervention	148	1·1 (0·9)	0·4 (0·7)	−0·8 (0·8)	..	..	..
Control	148	1·1 (0·8)	1·3 (0·9)	0·2 (0·5)	..	..	..
Number of prescribed antihypertensive medications	..	..	..	..	−0·58 (−0·75 to −0·42)	0·0001	0·05
Intervention	148	1·0 (1·2)	0·5 (0·7)	−0·6 (1·0)	..	..	..
Control	148	1·0 (1·1)	1·0 (1·0)	0·1 (0·5)	..	..	..
Systolic blood pressure (mm Hg)	..	..	..	..	−0·6 (−4·5 to 3·3)	0·7710	0·08
Intervention	128	134·3 (17·6)	133·0 (16·3)	−1·3 (18·3)	..	..	..
Control	147	137·5 (15·8)	135·8 (14·6)	−1·7 (13·7)	..	..	..
Quality of life‡	..	..	..	..	6·4 (2·5 to 10·3)	0·0012	0·01
Intervention	125	66·4 (19·2)	73·7 (19·0)	7·2 (21·3)	..	..	..
Control	147	72·0 (16·9)	69·1 (15·6)	−2·9 (15·5)	..	..	..

Intervention effects reported as estimated mean differences (intervention minus control), based on a mixed-effects linear regression model adjusted for treatment group, baseline value, study centre (Tyneside or Scotland), and practice list size (≤5700 or >5700) as fixed effects, and general practice as a random effect. ICC=intraclass correlation coefficient. *Number of participants with data available at baseline and 12 months for each outcome. †Numbers of participants prescribed no, one, or two or more oral antidiabetic medications at 12 months were 109 (73%), 26 (18%), and 13 (9%), respectively, in the intervention group; and 27 (18%), 70 (47%), and 51 (34%), respectively, in the control group. ‡As measured by the EuroQol 5 Dimensions visual analogue scale.

Table 2: **Key secondary and other outcomes**

Discussion

Our findings confirm that type 2 diabetes of up to 6 years' duration is not necessarily a permanent, lifelong condition. Weight loss sufficient to achieve remission can be attained in many individuals by use of an evidence-based structured weight management programme delivered in a non-specialist community setting by routine primary care staff. Just less than a quarter of participants in the intervention group achieved weight loss of 15 kg or more at 12 months, half maintained more than 10 kg loss, and almost half had remission of diabetes, off antidiabetic medication. This result is substantially in excess of the 22% remission rate that was deemed a priori to be clinically important, and that informed the power calculation. Remission was closely related to the degree of weight loss maintained at 12 months, with achievement in 86% of participants with at least 15 kg weight loss, and 73% of those with weight loss of 10 kg or more. 28% of all eligible individuals volunteered to participate,[17] and 79% completed the intensive total diet replacement phase, in keeping with evidence showing that people with type 2 diabetes rank reversal of the disease as their top priority for research.[18]

The approach used in DiRECT differs from many weight management treatments in its structured design, with a focus from the outset on the need for long-term maintenance of weight loss. Individual flexibility is important to optimise individual results. Durations of the weight loss and food reintroduction phases were allowed to vary within reasonably wide boundaries. The need for flexibility during the total diet replacement phase was largely for social reasons, and during food reintroduction to allow individuals longer, if needed, to adapt to new normal eating habits. Behavioural change methods were incorporated in the weight loss maintenance phase, including elements of cognitive behavioural therapy. Participants in the intervention group were advised to continue and not decrease their usual daily activities. During food reintroduction and weight loss maintenance, participants were advised on strategies to raise physical activity towards a target of 15 000 steps per day. It was recognised that this target was unlikely to be achieved by many, and objectively measured physical activity showed no increase in physical activity in either group between baseline and 12 months, which underlines the difficulty this

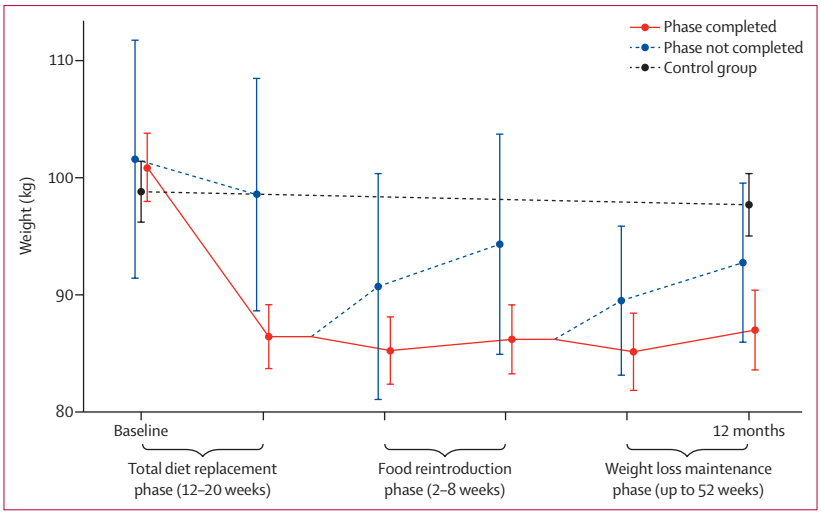

Figure 3: **Change in weight of participants who remained in the trial and those who dropped out during each phase of the intervention**
Error bars represent 95% CIs.

	All (n=306)	Intervention group (n=157)	Control group (n=149)
Number of serious adverse events	11	9	2
Number of participants with any serious adverse event	9 (3%)	7 (4%)	2 (1%)
Cardiac disorders*	1 (<1%)	1 (1%)	0
Angina pectoris†	1 (<1%)	1 (1%)	0
Gastrointestinal disorders*	2 (1%)	2 (1%)	0
Abdominal pain†	1 (<1%)	1 (1%)	0
Abdominal strangulated hernia†	1 (<1%)	1 (1%)	0
Hepatobiliary disorders*	1 (<1%)	1 (1%)	0
Cholelithiasis†	1 (<1%)	1 (1%)	0
Infections and infestations	2 (1%)	1 (1%)	1 (1%)
Urinary tract infection†	1 (<1%)	1 (1%)	0
Wound infection†	1 (<1%)	0	1 (1%)
Injury, poisoning, and procedural complications*	2 (1%)	2 (1%)	0
Incisional hernia†	1 (<1%)	1 (1%)	0
Synovial rupture†	1 (<1%)	1 (1%)	0
Nervous system disorders*	2 (1%)	1 (1%)	1 (1%)
Dizziness†	1 (<1%)	1 (1%)	0
Presyncope†	1 (<1%)	1 (1%)	0
Seventh nerve paralysis†	1 (<1%)	0	1 (1%)

Data are n (%). *Classified by Medical Dictionary for Regulatory Activities system organ class. †Classified by preferred term.

Table 3: **Serious adverse events**

population have in maintaining increased activity. The weight changes seen at 12 months in the intention-to-treat population of the present study are similar to those reported in a Counterweight-Plus feasibility study (–9·5 kg in intention-to-treat analyses with baseline observation carried forward [n=91])[12] and in an audit of its use in routine primary care, including patients with type 2 diabetes (–10·5 kg in intention-to-treat analyses with imputed data [n=217]).[19] Findings from Franz and colleagues' meta-analysis[20] showed an average weight change of about 10 kg at 12 months from interventions with very low calorie diets. Weight losses in DiRECT are greater than those reported in similar published studies of people with type 2 diabetes. The Counterbalance study[6] reported similar weight loss, but was intensively managed with very low calorie diet in a research centre. Look AHEAD[21] delivered a heavily supported programme in specialist centres, combining physical activity and dietary programme, and achieved a mean weight loss of 8·6 kg. Remission of type 2 diabetes was not the primary outcome in Look AHEAD, but was observed in 11·5% of participants after 1 year and 7·5% after 4 years, with 9·2% achieving remission for at least 2 years.[22] A Finnish study[23] showed improved glucose control and reduced use of diabetes medication after years 1 and 2 of a lifestyle intervention. More than 25 years ago, Wing and colleagues[24] reported improvement of HbA_{1c}, from a higher baseline level than DiRECT, after a very low calorie diet intervention under specialist supervision, with mean weight loss at 12 months of 8·6 kg. The present study differs importantly from most previous ones in that it was done under real-life conditions, delivered by the available local nurses or dietitians rather than by specialist staff. The study also included a greater proportion of men than normally seen in weight loss trials. Furthermore, no previous registered study has set remission of type 2 diabetes as a primary outcome.

Bariatric surgery has dominated discussions of type 2 diabetes remission as the most effective way of producing major weight loss.[8–10] However, this option comes at a high financial cost and with the risk of long-term problems, such as post-prandial hypoglycaemia, and micronutrient deficiencies that restrict acceptability.[25,26] The large numbers of people with type 2 diabetes makes it impossible to offer surgery to all people, even if this approach were financially possible and palatable to everyone. The essential mechanisms behind bariatric surgery are weight loss and decrease in body fat content, rather than any direct surgical effect.[27–31] The very large weight losses targeted by bariatric surgery are not essential for achievement of remission of type 2 diabetes, as shown by the present data. Changes in intra-organ fat content and β-cell function in a subgroup of the DiRECT cohort will be reported separately.

Weight loss leads to a rapid and marked fall in blood pressure, with risk of postural hypotension if anti-hypertensive drugs are continued. The acute fall in blood pressure with a low energy formula diet is greater than anticipated from reduced salt intake alone.[6] For that reason, all diuretic and antihypertensive medications were withdrawn at the start of the total diabetes replacement phase in participants in the intervention group, and only restarted if systolic blood

pressure exceeded 140 mm Hg. This approach resulted in 68% of the intervention group remaining off antihypertensive drugs at 12 months, with no increase in mean blood pressure. In terms of lipids, although only triglyceride concentrations declined, baseline cholesterol values were suppressed under guideline-driven statin prescriptions.

Quality of life improved significantly in the intervention group at 12 months, but was unchanged in the control group. The need to take antidiabetic medications was greatly decreased. The benefits to individuals[32] and the improved physical and psychological wellbeing accompanying substantial weight loss have previously been documented.[33] The present study was not designed or powered to evaluate effects on complications of diabetes. However, the clear improvement in HbA_{1c} values, which became non-diabetic in 46% of participants in the intervention group, if maintained, can reasonably be expected to reduce microvascular complications. In a post-hoc analysis of the Look AHEAD dataset, a 10% weight loss in the first year, similar to that in the DiRECT, was associated with a 21% decrease in occurrence of cardiovascular outcomes over a median follow-up of 10·2 years.[34] Even if diabetes recurs, there might be a legacy effect of a period of good glucose control, as suggested in the UK Prospective Diabetes Study.[35] Sudden restoration of normoglycaemia can precipitate worsening of diabetic retinopathy, although this outcome is rare when early or no retinopathy is present.[35] Nonetheless, if retinopathy is present at baseline, rescreening at 6 months is indicated.[35] It will be possible to determine the effects of DiRECT intervention by future analysis of the national retinopathy screening databases.

DiRECT thus offers considerable novel and clinically tractable information. The strengths of the study include a well defined evidence-based intervention and a robust cluster-randomised study design, managed by a well established clinical trials unit. The sample size exceeded the need for statistical power, and the remission rate of 46% greatly exceeded the level of 22% considered clinically important. Hence, the results are robust for the patient group under study. The sample had characteristics very similar to the general population of people with type 2 diabetes, so the results are likely to be generalisable.[17]

The study has some limitations. The racial and ethnic characteristics, while typical of the populations of Scotland and Tyneside, do not allow for unqualified extrapolation to other groups, such as south Asians, who tend to develop diabetes with less weight gain. There were limitations to the data that could be collected in the routine primary care setting; therefore, detailed body composition was not assessed.

Because the unit of randomisation was the primary care centre, participants were aware of their planned allocation to the control or intervention group; however, negligible bias seemed to result from this design on the basis of baseline group characteristics. It is not possible to exclude some contamination of the control group, with deliberate weight loss as a result of media publicity about the intervention during the study. Such contamination would have tended to attenuate the effects of the intervention.

Antidiabetic medications were stopped in the intervention group, but not in the control group. Withdrawal of antidiabetic medications might have been possible in some participants in the control group, but the study design was a comparison of the entire programme with current standard of care, under current guidelines. The dropout rate of 25% in the intervention group was an indication of non-acceptability for this proportion, but should be considered in relation to the overall effectiveness of the programme for a much greater proportion. The study design stipulated data collection from the control group only at baseline and 12 months, so intercurrent adverse events could not be assessed. Subsequent analyses might be able to examine routinely collected primary care data from both groups, including all prescriptions. Here we present only the numbers of different drugs prescribed at baseline and 12 months, and not dosage changes. Further detailed analysis of medication and dosage changes could be possible. We did collect information about serious adverse events in both groups, retrospectively at the 12 month assessments, and recorded only two, in the same participant, that might have been related to the intervention.

The data for physical activity should be viewed with caution because they were based on around half of all participants in each group for whom the data were complete.

Four participants in the intervention group who had diabetes remission had received a short rescue plan in the total diet replacement phase because of weight regain within 60 days of their 12 month assessment. We cannot exclude a carryover acute effect of the rescue plans suppressing HbA_{1c} in these participants, but believe any such effect would have been very small and unlikely to affect the study conclusions. Two of the 12 participants who received rescue plans within 60 days of their 12 month assessment achieved more than 15 kg weight loss.

The conclusions reported here apply to people with type 2 diabetes diagnosed within the previous 6 years, and existing evidence has shown that remission is less likely with longer durations of disease.[6,8]

This large primary care-based trial shows that a professionally supported intensive weight management programme is attractive to many people early in the course of type 2 diabetes. The programme allowed almost half of participants to revert to a non-diabetic state, off antidiabetic drugs at 12 months, and 68% stopped antihypertensive medications with no rise in blood pressure. Follow-up of this cohort to establish longer term outcomes will continue to at least 4 years. Continued work on optimising

the maintenance of weight loss would be useful; however, our results should pave the way for this type of intervention to be considered in the routine care of patients with type 2 diabetes who wish to attain diabetes remission.[36]

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 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. RS and MT developed methodology, and analysed and interpreted the physical activity data. MEJL, RT, WSL, NS, and AM drafted the manuscript. All authors critically reviewed and revised the manuscript, and have read and approved the final version.

Declaration of interests

NB reports funding from Counterweight and Cambridge Weight Plan, outside the submitted work. MEJL reports personal fees from Counterweight during the conduct of the study, and non-financial support from Cambridge Weight Plan outside the submitted work. MT is co-founder and Director of Changing Health. GT reports funding from Cambridge weight plan outside the submitted work. HMR reports employment by Counterweight during the study, and is shareholder in Counterweight outside the submitted work. NS reports grants and personal fees from Boehringer Ingelheim; personal fees from Janssen, Eli Lilly, and Novo Nordisk; and grants from AstraZeneca, outside the submitted work. LM reports employment by Counterweight during the conduct of study, and employment from Cambridge Weight Plan outside the submitted work. All other authors declare no competing interests.

Acknowledgements

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

References

1 Public Health England National Cardiovascular Intelligence Network. 3·8 million people in England now have diabetes. Sept 13, 2016. https://www.gov.uk/government/news/38-million-people-in-england-now-have-diabetes (accessed Nov 14, 2017).
2 WHO. Global report on diabetes. 2016. http://www.who.int/diabetes/global-report/en/ (accessed Oct 19, 2017).
3 Wright AK, Kontopantelis E, Emsley R, et al. Life expectancy and cause-specific mortality in type 2 diabetes: a population-based cohort study quantifying relationships in ethnic subgroups. *Diabetes Care* 2017; **40:** 338–45.
4 Taylor R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. *Diabetologia* 2008; **51:** 1781–89.
5 Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011; **54:** 2506–14.
6 Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very Low calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. *Diabetes Care* 2016; **39:** 158–65.
7 Henry RR, Schaeffer L, Olefsky JM. Glycaemic effects of intensive caloric restriction and isocaloric refeeding in non-insulin dependent diabetes mellitus. *J Clin Endocrinol Metab* 1985; **61:** 917–25.
8 Sjostrom L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014; **311:** 2297–2304.
9 Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. *J Intern Med* 2013; **273:** 219–34.
10 Schauer PR, Burguera B, Ikramuddin S, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. *Ann Surg* 2003; **238:** 467–84.
11 Leslie WS, Ford I, Sattar N, et al. The Diabetes Remission Clinical Trial (DiRECT): protocol for a cluster randomised trial. *BMC Fam Pract* 2016; **17:** 20.
12 Lean M, Brosnahan N, McLoone P, et al. Feasibility and indicative results from a 12-month low-energy liquid diet treatment and maintenance programme for severe obesity. *Br J Gen Pract* 2013; **63:** e115–124.
13 Doherty A, Jackson D, Hammerla N, et al. Large scale population assessment of physical activity using wrist worn accelerometers: the UK Biobank Study. *PLoS One* 2017; **12:** e0169649.
14 van Hees VT, Sabia S, Anderson KN, et al. A novel, open access method to assess sleep duration using a wrist-worn accelerometer. *PLoS One* 2015; **10:** e0142533.
15 National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. 2015 https://www.nice.org.uk/guidance/ng28 (accessed Oct 30, 2017).
16 Scottish Intercollegiate Guideline Network. Management of diabetes: a national clinical guideline. 2010. http://www.sign.ac.uk/assets/sign116.pdf (accessed Oct 30, 2017).
17 Taylor R, Leslie WS, Barnes AC, et al. Clinical and metabolic features of the randomised controlled Diabetes Remission Clinical Trial (DiRECT) cohort. *Diabetologia* 2017; published online Nov 30. https://doi.org/10.1007/s00125-017-4503-0.
18 Finer S, Robb P, Cowan K, Daly A, Robertson E, Farmer A. Top ten research priorities for type 2 diabetes: results from the Diabetes UK–James Lind Alliance Priority Setting Partnership. *Lancet Diabetes Endocrinol* 2017; published online Oct 27. http://dx.doi.org/10.1016/S2213-8587(17)30324-8.
19 Ross H, Brosnahan NT, Bell-Higgs A, Govan L, McCombie L, Lean MEJ. Counterweight-Plus: an intensive, non-surgical option for severe obesity. October, 2017. https://obesityweek.com/abstract/counterweight-plus-an-intensive-non-surgical-option-for-severe-obesity/(accessed Nov 29, 2017).
20 Franz M, Vanwormer JJ, Crain L et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1 year follow up. *J Am Diet Assoc* 2007; **107:** 1755–67.
21 Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity* 2014; **22:** 5–13.
22 Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012; **308:** 2489–96.
23 Uusitupa MI. Early lifestyle intervention in patients with non-insulin-dependent diabetes mellitus and impaire glucose tolerance. *Ann Med* 1996; **28:** 445–49.
24 Wing RR, Marcus MD, Salata R, Epstein LH, Miaskiewicz S, Blair EH. Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. *Arch Intern Med* 1991; **151:** 1334–40.
25 Meier JJ, Butler AE, Galasso R, Butler PC. Hyperinsulinemic hypoglycemia after gastric bypass surgery is not accompanied by islet hyperplasia or increased beta-cell turnover. *Diabetes Care* 2006; **29:** 1554–59.
26 Vecht J, Masclee AA, Lamers CB. The dumping syndrome. Current insights into pathophysiology, diagnosis and treatment. *Scand J Gastroenterol Suppl* 1997; **223:** 21–27.

27 White MG, Shaw JAM, Taylor R. Type 2 diabetes: the pathologic basis of reversible beta-cell dysfunction. *Diabetes Care* 2016; **39:** 2080–88.

28 Talchai C, Xuan S, Lin HV, Sussel L, Accili D. Pancreatic beta cell dedifferentiation as a mechanism of diabetic beta cell failure. *Cell* 2012; **150:** 1223–34.

29 Pinnick K, Neville M, Clark A, Fielding B. Reversibility of metabolic and morphological changes associated with chronic exposure of pancreatic islet beta-cells to fatty acids. *J Cell Biochem* 2010; **109:** 683–92.

30 Lingvay I, Guth E, Islam A, Livingston E. Rapid improvement in diabetes after gastric bypass surgery. *Diabetes Care* 2013; **36:** 2741–47.

31 Steven S, Hollingsworth KG, Small P, et al. Weight loss decreases excess pancreatic triacylglycerol specifically in type 2 diabetes. *Diabetes Care* 2016; **39:** 158–65.

32 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359:** 1577–89.

33 Rehackova L, Araújo-Soares V, Adamson AJ, Stevens S, Taylor R, Sniehotta FF. Acceptability of a very low energy diet in type 2 diabetes: patient experiences and behaviour regulation. *Diabetic Med* 2017; **34:** 1554–67.

34 The Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2016; **4:** 913–921.

35 Arun CS, Pandit R, Taylor R. Long-term progression of retinopathy after initiation of insulin therapy in Type 2 diabetes: an observational study. *Diabetologia* 2004; **47:** 1380–84

36 McCombie L, Leslie W, Taylor R, Kennon B, Sattar N, Lean MEJ. Beating type 2 diabetes into remission. *BMJ* 2017; **358:** j4030.