Primary care weight-management for type 2 diabetes: the cluster-randomised Diabetes Remission Clinical Trial (DiRECT)

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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/m^2, 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.

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. 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,[7,8,9,10] 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.

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/m^2. 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 m^2, 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 pre-specified 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 pre-specified 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 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, Fig 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 p2). Sensitivity analyses using alternative assumptions regarding missing data for weight at 12 months gave similar results (appendix pp2,3) 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];Fig 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 p4).

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The appendix (p10) shows the number of participants who self-reported adverse events that were pre-specified 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 p10). 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 p10). Information about symptoms was collected only from participants in the intervention group.

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 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.[8,9,10] 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.[27,28,29,30,31] 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 antihypertensive 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.

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1. Public Health England (PHE) National Cardiovascular Intelligence Network. https://www.gov.uk/government/news/38-million-people-in-england-now-have-diabetes accessed 14th November 2017
2. WHO (2016) Global Report on Diabetes. http://www.who.int/diabetes/global-report/en/ accessed 19 October 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**: 338-345
4. Taylor R. Pathogenesis of Type 2 diabetes: Tracing the reverse route from cure to cause. *Diabetologia* 2008; **51**: 1781-1789
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**: 2506-2514
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**: 158-165
7. Henry RR, Schaeffer L, Olefsky JM. Glycaemic effects of intensive caloric restriction and isocaloric refeeding in non-insulin dependent diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism* 1985; **61**: 917-925
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**: 219-234

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**: 467-484
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, Plötz T, et al. Large Scale Population Assessment of Physical Activity Using Wrist Worn Accelerometers: The UK Biobank Study. *PLoS One* 2017 **12**(2):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**(11):e0142533.
15. National Institute for Health and Care Excellence Type 2 diabetes in adults: management 2015 https://www.nice.org.uk/guidance/ng28 Accessed 30.10.2017
16. Scottish Intercollegiate Guideline Network. Management of Diabetes: A national clinical guideline. 2010 http://www.sign.ac.uk/assets/sign116.pdf Accessed 30.10.2017
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 (in press)
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 Online First DOI:http://dx.doi.org/10.1016/S2213-8587(17)30324-8 accessed 13.11.2017
19. Ross H, Brosnahan NT, Bell-Higgs A, Govan L, McCombie L, Lean MEJ. Counterweight-Plus, An Intensive, Non-Surgical Option For Severe Obesity. ObesityWeek.com. 2017 Late Breaking Posters https://obesityweek.com/abstract/counterweight-plus-an-intensive-non-surgical-option-for-severe-obesity/

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 AmDietAssoc* 2007;**107**:1755-1767.
21. LookAhead 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, Clark JM, Delahanty LM, Bantle J, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA : the journal of the American Medical Association. 2012;308(23):2489-96
23. Uusitupa MIJ. Early Lifestyle Intervention in Patients with Non-insulin-dependent Diabetes Mellitus and Impaire Glucose Tolerance. Annals of Med 28: 445-449; 2006 http://dx.doi.org/10.3109/07853899608999106 accessed 13.11.201
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(7):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**: 1554-1559
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**: 2080-2088
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**: 1223-1234
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**: 683-692

30. Lingvay I, Guth E, Islam A, Livingston E. Rapid improvement in Diabetes after Gastric Bypass Surgery. *Diabetes Care* 2013; **36**:2741–2747
31. Steven S, Hollingsworth KG, Small P, et al. Weight loss decreases excess pancreatic triacylglycerol specifically in type 2 diabetes. *Diabetes Care* 2016; **39**: 158-165
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**: 1577-1589
33. Rehackova L, Araujo-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**:1554-1567
34. The LookAHEAD 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. *The Lancet Diabetes & Endocrinology* 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**: 1380-1384
36. McCombie L, Leslie W, Taylor R, Kennon B, Sattar N, Lean MEJ. Beating type 2 diabetes into remission. *BMJ* 2017 358:j4030 https://doi.org/10.1136/bmj.j4030 accessed 13.11.2017

Figure 1: Trial Profile

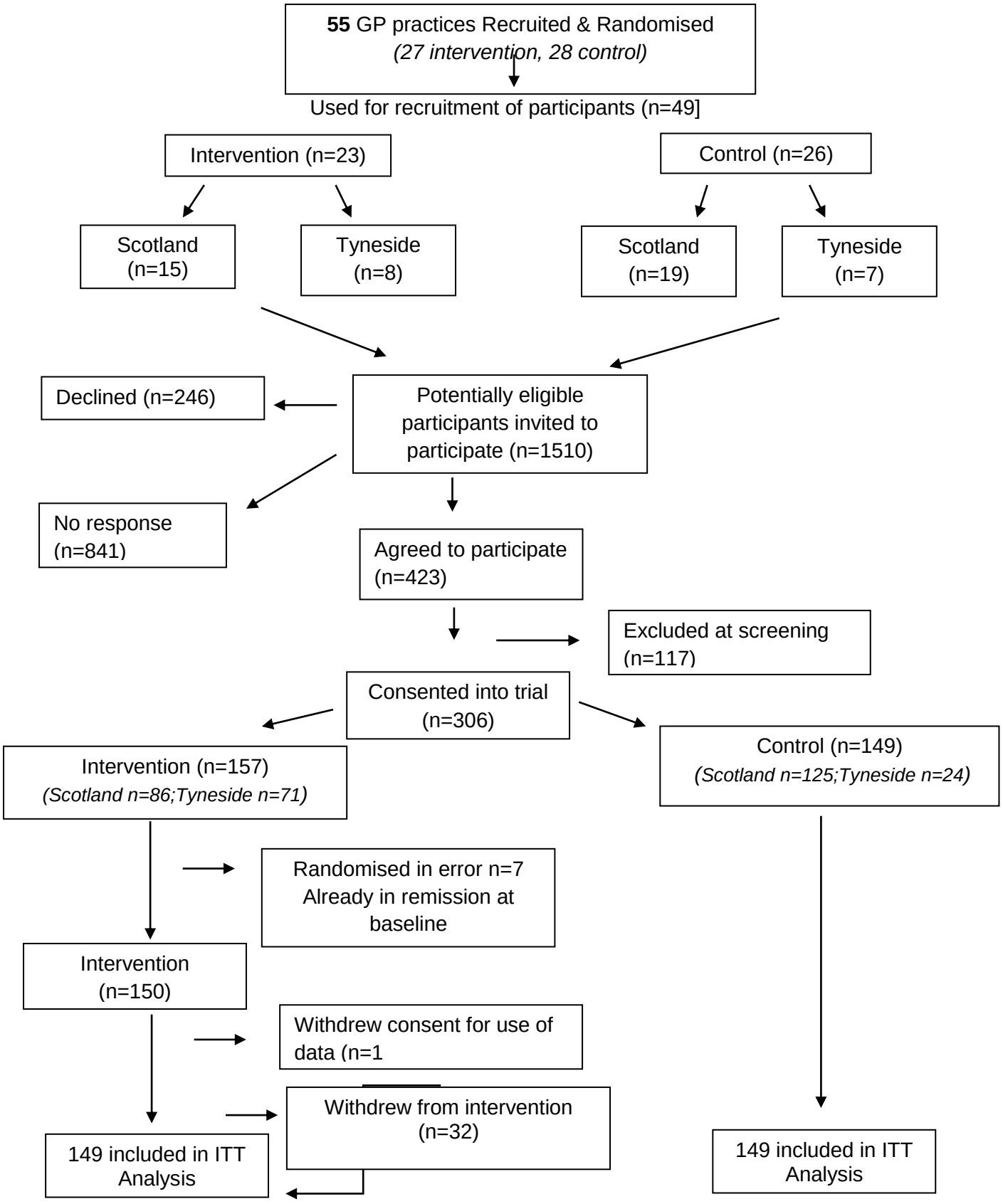


Figure 2: Primary outcomes and remission of diabetes in relation to weight loss at 12 months.

A: First co-primary outcome, achievement of ≥15kg weight loss at 12 months, 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 at 12 months (both randomised groups combined).

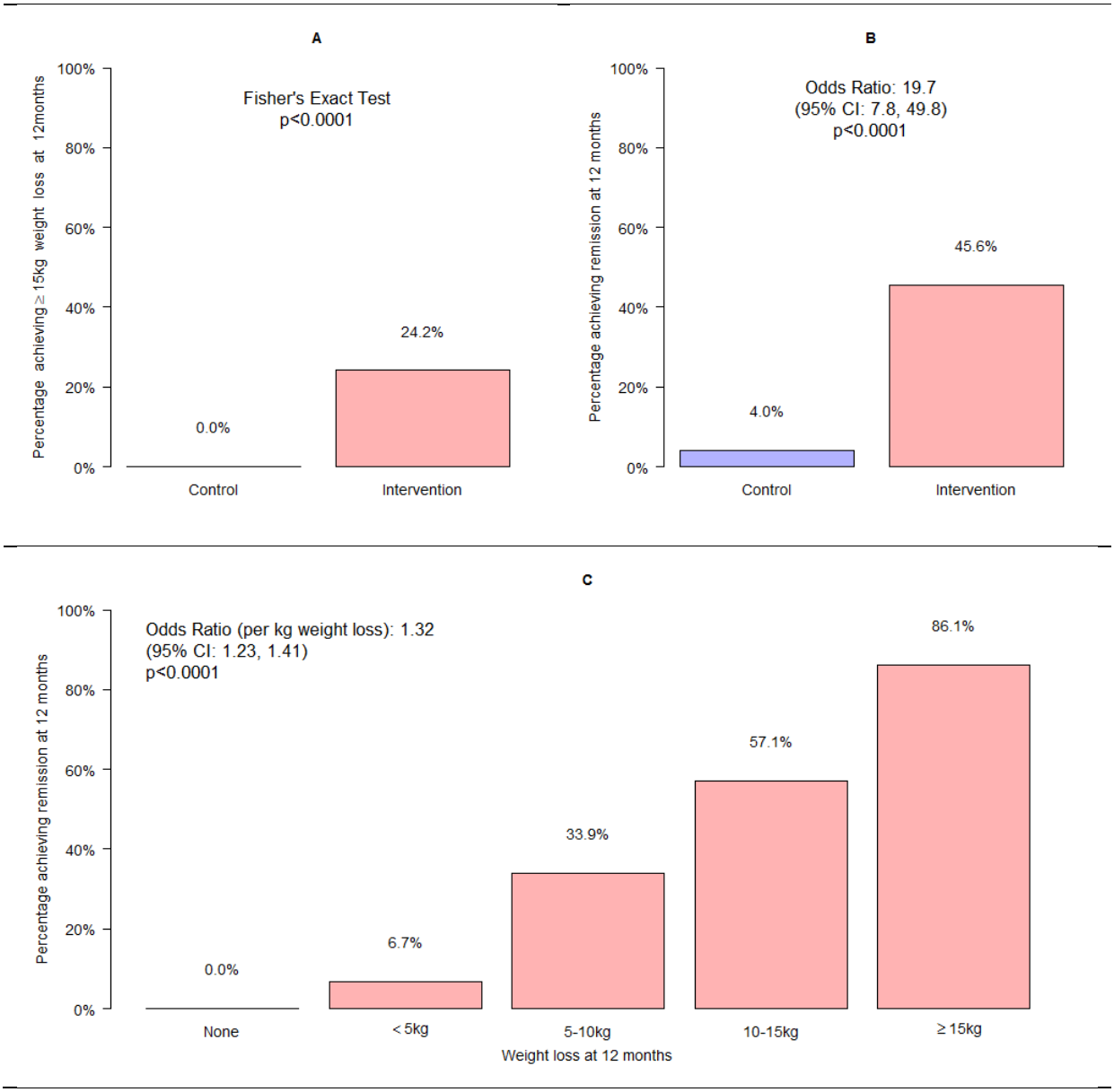
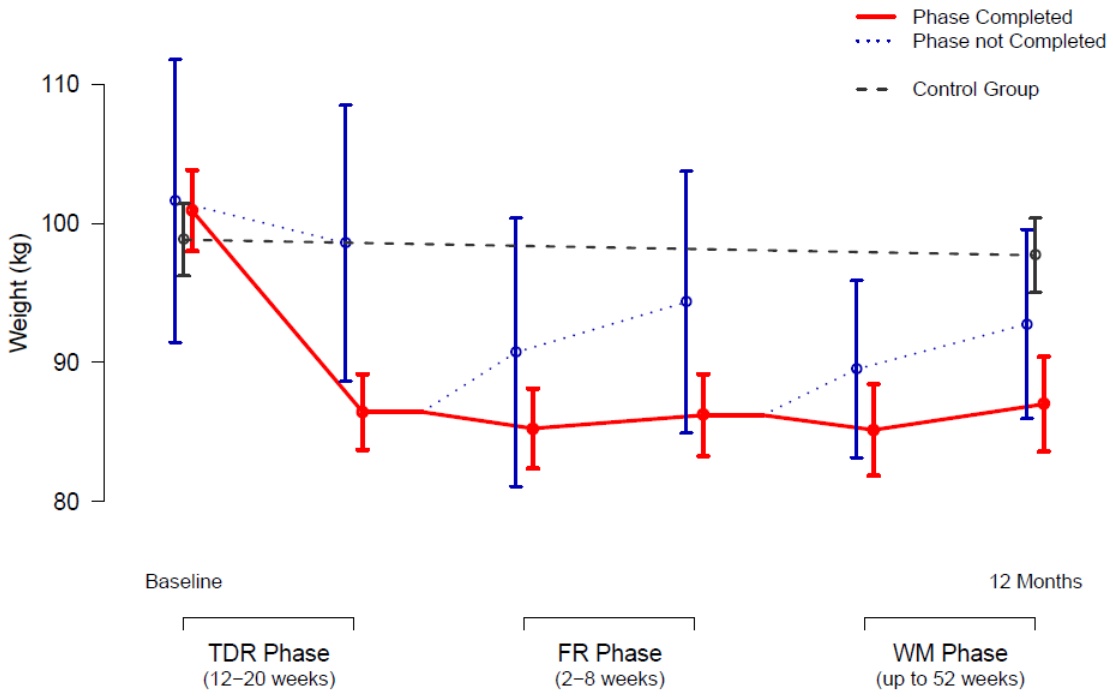


Fig 3: Changes in weight of participants who remained in the trial and those who dropped out during each phase of the intervention



Error bars represent 95% CI

Table 1: Baseline characteristics

	Control n=149	Intervention n=149
Sex (Male)	93 (62·4)	83 (55·7)
Ethnicity (White)	147 (98·7)	146 (98·0)
Age (years)	55·9 (7·3)	52·9 (7·6)
Weight (kg)	98·8 (16·1)	101·0 (16·7)
BMI (kg/m^2)	34·2 (4·3)	35·1 (4·5)
Waist (cm)	106·5 (8·9)	107·5 (8·4)
Systolic BP (mmHg)	137·2 (16·0)	132·7 (17·5)
Diastolic BP (mmHg)	85·5 (8·8)	84·6 (10·2)
Years since diabetes diagnosis: mean (SD) [range]	3·0 (1·8) [0.2, 6.0]	3·2 (1·7) [0.0, 6.0]
HbA1c (mmol/mol)	58 (11·5)	60 (13·7)
HbA1c (%)	7·5 (1·05)	7·7 (1·25)
Fasting Glucose (mmol/l)	8·82 (2·54)	9·22 (3·29)
Prescribed oral anti-diabetic medication	115 (77·2)	111 (74·5)
Number of oral anti-diabetic medications		
0	34 (22·8)	38 (25·5)
1	79 (53·0)	65 (43·6)
2+	36 (24·2)	46 (30·9)
Hypertension	88 (59·1)	81 (54·4)
Any CVD	24 (16·1)	13 (8·7)
Prescribed statins	100 (67·1)	93 (62·4)
Albumin/Creatinine Ratio (mg/mmol)[(a)]	1·19 (2·4)	3·16 (9·4)
Microalbuminuria[(b)]	11 (7·4)	28 (19·4)
eGFR (mL/min/1·73 m^2)	95·8 (25·2)	101·5 (23·9)
Total Cholesterol (mmol/l)	4·31 (1·2)	4·34 (1·1)
HDL Cholesterol (mmol/l)	1·16 (0·31)	1·08 (0·25)
Triglycerides (mmol/l) – Median (IQR)	1·66 (1·3, 2·5)	1·83 (1·4, 2·4)
Retinopathy	21 (14·1)	14 (9·4)
Neuropathy	2 (1·3)	2 (1·3)
eGFR <60 ml/min/l·73m^2	6 (4·1)	3 (2·1)
Microvascular complications	26 (17·6)	19(13·2)

Data are mean (SD) or N (%) unless otherwise stated. (a): ACR values <0·5 imputed as 0·25. (b) Microalbuminuria defined as ACR≥3·5 (female) or ACR≥2·5 (male)

Table 2: Key secondary and other outcomes

		N	Mean (SD)			Intervention Effect			ICC
			Baseline	12months	Change	Estimate	95% CI	p-value	
Weight (kg)	Intervention	137	100·4 (16·5)	90·4 (16·4)	-10·0 (8·0)	-8·8	(-10·3, -7·3)	p<0·0001	<0·01
	Control	148	98·7 (16·1)	97·7 (16·4)	-1·0 (3·7)				
HbA1c (mmol/mol)	Intervention	138	60·2 (12·7)	50·6 (13·3)	-9·6 (15·4)	-9·3	(-12·1, -6·5)	p<0·0001	<0·01
	Control	148	58·2 (11·6)	59·6 (12·1)	1·4 (11·6)				
HbA1c (%)	Intervention	138	7.7 (1.2)	6.8 (1.2)	-0.9 (1.4)	-0.85	(-1.10, -0.59)	p<0·0001	<0·01
	Control	148	7.5 (1.1)	7.6 (1.1)	0.1 (1.1)				
Number of prescribed oral antidiabetic medications[(a)]	Intervention	148	1·1 (0·9)	0·4 (0·7)	-0·8 (0·8)	-0·97	(-1·11, -0·84)	p<0·0001	<0·01
	Control	148	1·1 (0·8)	1·3 (0·9)	0·2 (0·5)				
Number of prescribed antihypertensive medications	Intervention	148	1·0 (1·2)	0·5 (0·7)	-0·6 (1·0)	-0·58	(-0·75, -0·42)	p<0·0001	0·05
	Control	148	1·0 (1·1)	1·0 (1·0)	0·1 (0·5)				
Systolic blood pressure (mmHg)	Intervention	128	134·3 (17·6)	133·0 (16·3)	-1·3 (18·3)	-0·6	(-4·5, 3·3)	p=0·7710	0·08
	Control	147	137·5 (15·8)	135·8 (14·6)	-1·7 (13·7)				
Quality of Life EQ-5D VAS	Intervention	125	66·4 (19·2)	73·7 (19·0)	7·2 (21·3)	6·4	(2·5, 10·3)	p=0·0012	0·01
	Control	147	72·0 (16·9)	69·1 (15·6)	-2·9 (15·5)				

Intervention effects reported as estimated mean differences (Intervention-Control), based on mixed effects linear regression model, adjusted for randomised group, baseline value, 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 baseline and 12 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%).

Table 3: Serious Adverse Events

		All	Control	Intervention
Number of Participants		306	149	157
Number of SAEs		11	2	9
Number (%) of participants with any SAE		9 (2.9%)	2 (1.3%)	7 (4.5%)
Number (%) of participants with any SAEs,classified by MedDRA System Organ Class (SOC) and Preferred Term (PT):				
SOC:	Cardiac disorders	1 (0.3%)	0 (0.0%)	1 (0.6%)
PT:	Angina pectoris	1 (0.3%)	0 (0.0%)	1 (0.6%)
SOC:	Gastrointestinal disorders	2 (0.7%)	0 (0.0%)	2 (1.3%)
PT:	Abdominal pain	1 (0.3%)	0 (0.0%)	1 (0.6%)
	Abdominal strangulated hernia	1 (0.3%)	0 (0.0%)	1 (0.6%)
SOC:	Hepatobiliary disorders	1 (0.3%)	0 (0.0%)	1 (0.6%)
PT:	Cholelithiasis	1 (0.3%)	0 (0.0%)	1 (0.6%)
SOC:	Infections and infestations	2 (0.7%)	1 (0.7%)	1 (0.6%)
PT:	Urinary tract infection	1 (0.3%)	0 (0.0%)	1 (0.6%)
	Wound infection	1 (0.3%)	1 (0.7%)	0 (0.0%)

SUPPLEMENTARY APPENDIX

Figure S1: Primary outcomes and remission of diabetes in relation to weight loss at 12 months.
A: First co-primary outcome, achievement of ≥15kg weight loss at 12 months, 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 at 12 months (both randomised groups combined).

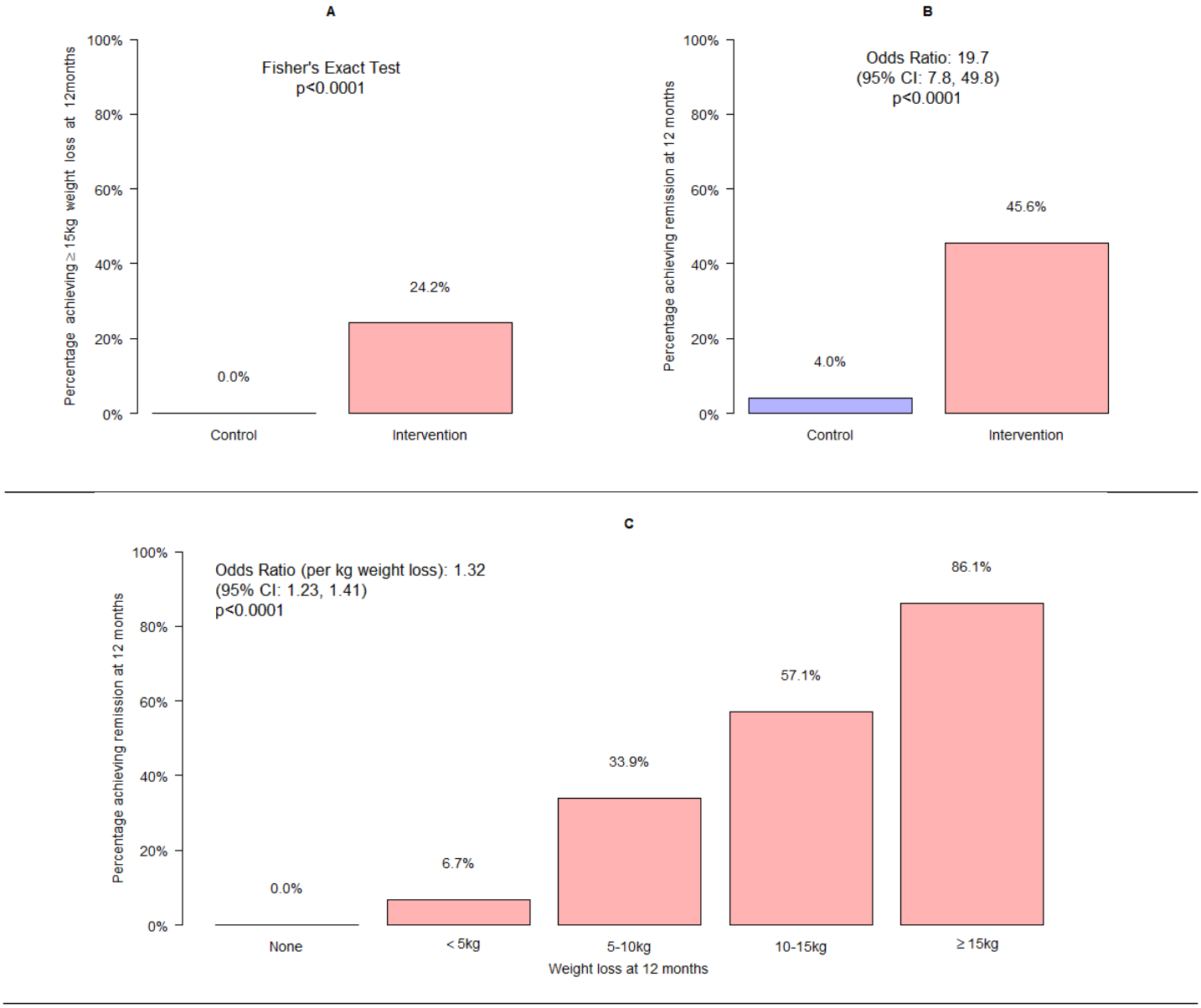


Table S1: Further analyses of secondary outcome measures and other outcomes in the intervention and control groups at baseline and 12 months

		N	Mean (SD)			Intervention Effect (Relative)			ICC
			Baseline	12months	Change	Estimate	95% CI	p-value	
Percentage weight change from baseline[(a)]	Intervention	137		-9·9 (7·6)		-8·8	(-10·2, -7·3)	p<0·0001	0·01
	Control	148		-1·1 (3·8)					
BMI (kg/m^2)	Intervention	137	35·0 (4·5)	31·5 (4.9)	-3·5 (2.8)	-3·0	(-3·5, -2·5)	p<0·0001	0·01
	Control	148	34·2 (4·3)	33·8 (4·5)	-0·4 (1.3)				
Number of other prescribed medications (not oral antidiabetic or antihypertensive)	Intervention	148	3·5 (3·0)	4·0 (3·9)	0·5 (2·0)	-0·08	(-0·49, 0·33)	p=0·7036[(b)]	<0·01
	Control	148	3·6 (3·4)	4·2 (3·7)	0·6 (1·4)				
Diastolic blood pressure (mmHg)	Intervention	128	84·8 (10·2)	83·5 (9·5)	-1·3 (10·3)	-0·4	(-2·5, 1·6)	p=0·6863	<0·01
	Control	147	85·5 (8·8)	84·5 (8·9)	-1·1 (10·1)				
Quality of Life EQ-5D health utility score	Intervention	125	0·806 (0·279)	0·793 (0·278)	-0·013 (0·211)	0·025	(-0·023, 0·073)	p=0·3146[(c)]	<0·01
	Control	147	0·799 (0·282)	0·759 (0·302)	-0·040 (0·203)				

Intervention effects reported as estimated mean differences (Intervention-Control), based on mixed effects linear regression model, adjusted for randomised group, baseline value[(a)], 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 baseline and 12 months for each outcome. ICC: Intraclass Correlation Coefficient.

(a): Effect estimate for percentage weight change includes adjustment for baseline weight

Some model residuals showed signs of non-Normal distribution:

(b): Results confirmed using non-parametric test of 12 month values (p=0.37) and change from baseline (p=0.053)

(c): Results confirmed using non-parametric test of 12 month values (p=0.33) and change from baseline (p=0.39)

Table S2: Weight at baseline and 12 months, under alternative assumptions regarding missing data

		N	Mean (SD)			Intervention Effect			ICC
			Baseline	12months	Change	Estimate	95% CI	p-value	
Complete Data (as in Table 2)	Intervention	137	100·4 (16·5)	90·4 (16·4)	-10·0 (8·0)	-8·8	(-10·3, -7·3)	p<0·0001	<0·01
	Control	148	98·7 (16·1)	97·7 (16·4)	-1·0 (3·7)				
IMPUTATION OF MISSING WEIGHTS									
Conservative (Return to Baseline)	Intervention	149	101·0 (16·7)	91·8 (17·1)	-9·2 (8·1)	-8·0	(-9·5, -6·5)	p<0·0001	<0·01
	Control	149	98·8 (16·1)	97·8 (16·4)	-1·0 (3·7)				
Optimistic (Last Observation Carried Forward)	Intervention	149	101·0 (16·7)	91·3 (16·8)	-9.7 (8·0)	-8·4	(-9·9, -6·9)	p<0·0001	<0·01
	Control	149	98·8 (16.1)	97.8 (16·4)	-1.0 (3·7)				
Realistic (see below)	Intervention	149	101·0 (16.7)	91·6 (17·0)	-9·4 (8·0)	-8·2	(-9·6, -6·7)	p<0·0001	<0·01
	Control	149	98·8 (16.1)	97·8 (16.4)	-1·0 (3·7)				

Intervention effects reported as estimated mean differences (Intervention-Control), based on mixed effects linear regression model, adjusted for randomised group, baseline value, 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 baseline and 12 months for each outcome. ICC: Intraclass Correlation Coefficient.

Imputation options:

- Conservative (Return to Baseline): missing 12 month weights imputed as the baseline value
- Optimistic (LOCF): missing 12 month weights imputed as the last recorded weight. For intervention patients, this could be during a treatment visit; for control patients, this will be the baseline value
- Realistic: missing 12 month weights imputed as the mean value from other patients in the same randomised group who did not attend the 12 month visit, but for whom the weight was obtained from GP records

Table S3: Changes in weight during each treatment phase. Data during TDR phase reported for all participants who started TDR; data during FR phase reported for all participants who successfully completed TDR; data during WLM phase reported for all participants who successfully completed FR (plus one patient who progressed directly from TDR to WLM). ”End of TDR” and “End of FR” weights refer to the final weight recorded at a study treatment visit during each phase.

		Completed Phase	Not Completed Phase	Difference[(a)] (95% CI), p-value
Weight During TDR Phase (for those who started TDR phase)				
	N	128	15	
Baseline	Mean (SD)	100·9 (16·7)	101·6 (18·4)	-0·7 (-9·7, 8·3), p=0·8797
End of TDR	Mean (SD)	86·4 (15·6)	98·6 (17.9)	-12·1 (-20·6, -3·7), p=0·0050
Change during TDR	Mean (SD) [95% CI]	-14·5 (6·0) [-15·5, -13·4]	-3·0 (3·6) [-5·0, -1·0]	-11·5 (-14·5, -8·6), p<0·0001
Weight During FR Phase (for those who progressed from TDR to FR)				
	N	107	20	
End of TDR	Mean (SD)	85·2 (15·0)	92·0 (17·7)	-5.5 (-13·4, 2·5), p=0·1779
End of FR	Mean (SD)	86·2 (15·4)	95·2 (17·1)	-8.1 (-16·2, 0·0), p=0·0488
Change during FR	Mean (SD) [95% CI]	1·0 (3·2) [0·3, 1·6]	3·2 (2·3) [2·1, 4·3]	-2·7 (-4·3, -1.1), p=0·0010
Weight During WLM Phase (for those who progressed from TDR to FR to WLM, or directly from TDR to WLM)				
	N	78	30	
End of FR	Mean (SD)	85·1 (14·6)	89·5 (17·0)	-4·4 (-10·8, 2·1), p=0·1851
12 Months	Mean (SD)	87·0 (15·1)	92·0 (17·2)	-5·0 (-11·6, 1·7), p=0·1424
Change during WLM	Mean (SD) [95% CI]	1·9 (2·9) [1·2, 2·5]	2·4 (3·0) [1·3, 3·5]	-0·6 (-1·8, 0·7), p=0·3809

(a): Difference (Completed – Not Completed) derived from two-sample t-test for differences at the start and end of each treatment phase. Differences in the change during each phase derived from a linear regression model of the change in weight, adjusted for weight at the start of the phase

Table S4: Secondary outcomes: binary outcomes in the intervention and control groups at baseline and 12 months

		N/Total (%)	Odds Ratio		
			Estimate	95% CI	p-value
Prescribed oral anti-diabetic medications	Intervention	39/148 (26·4%)	0·07	(0·03, 0·14)	p<0·0001
	Control	121/148 (81·8%)			
All Patients					
HbA_{1c} <48mmol/mol	Intervention	71/138 (48·6%)	7·02	(3·66, 13·46)	p<0·0001
	Control	23/148 (15·5%)			
HbA_{1c} <42mmol/mol	Intervention	40/138 (29·0%)	8·38	(3·49, 20·14)	p<0·0001
	Control	7/148 (4·7%)			
For those patients prescribed oral anti-diabetic medication at 12 months					
HbA_{1c} <48mmol/mol	Intervention	3/35 (8.6%)	0·55	(0·14, 2·09)	p=0·3797
	Control	17/121 (14.0%)			
HbA_{1c} <42mmol/mol	Intervention	1/35 (2.9%)	0·46	(0·05, 4·28)	p=0·4941
	Control	6/121 (5.0%)			
For those patients NOT prescribed oral anti-diabetic medication at 12 months					
HbA_{1c} <48mmol/mol	Intervention	68/103 (66.0%)	7·51	(2·40, 23·48)	p=0·0005
	Control	6/27 (22.2%)			
HbA_{1c} <42mmol/mol	Intervention	39/103 (37·9%)	15·40	(1·98, 120·12)	p=0·0091
	Control	1/27 (3.7%)			

Intervention effects reported as estimated odds ratios (Intervention:Control), based on mixed effects logistic regression model, adjusted for randomised group, study centre (Tyneside, Scotland), and practice list size (≤5700, >5700) as fixed effects, and GP practice as a random effect.
Total N varies by outcome depending on data availability

Table S5: Secondary outcomes: physical activity, sleep duration and efficiency in intervention and control groups at baseline and 12 months

		N	Mean (SD)			Intervention Effect (Intervention:Control)			Intra-class coefficient
			Baseline	12months	Change	Estimate	95% CI	p-value	
Sleep duration (minutes/day)	Intervention	73	421·4 (77·1)	423·1 (74·8)	2 (86)	8.2	(-13·2, 29.5)	p=0.4522[(a)]	0.02
	Control	74	441·7 (64.5)	427·8 (61·8	-14 (63)				
Sleep efficiency (%)	Intervention	73	72·7 (10.7)	71·9 (11·9)	-0.8 (13.8)	-1.21	(-4.76, 2.35	p=0.5066[(b)]	0.03
	Control	74	74·5 (9.0)	74·1 (9.3)	-0.3 (10.4)				
Sedentary time (minutes/day)	Intervention	73	188·3 (63·2)	180·6 (67·3)	-8 (71)	-5·9	(-25·7, 13·9)	p=0·5587	<0·01
	Control	77	177·5 (65·2)	180·8 (69·9)	3 (63)				
Light activity (minutes/day)	Intervention	73	117·5 (39·2)	117·9 (42·9)	0 (42)	3·0	(-8·8, 14·8)	p=0·6184	<0·01
	Control	77	109·6 (46·6)	110·8 (44·7)	1 (37)				
Moderate activity (minutes/day)	Intervention	73	51·0 (21·3)	51·2 (23·1)	0·1 (22·3)	0·81	(-5·80, 7·42)	p=0·8110	<0·01
	Control	77	48·1 (26·5)	48·9 (26·5)	0·7 (21·4)				
Vigorous activity (minutes/day)	Intervention	73	0·9 (0·7)	0·8 (0·9	-0·03 (0·91)	0·03	(-0·23, 0·28)	p=0·8402[(c)]	0·05
	Control	77	0·7 (0·6)	0·7 (0·7)	0·01 (0·64)				

Intervention effects reported as estimated mean differences (Intervention-Control), based on mixed effects linear regression model, adjusted for randomised group, baseline value, 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 baseline and 12 months for each outcome.

Some model residuals showed signs of non-Normal distribution:

(a): Results confirmed using non-parametric test of 12 month values (p=0.81) and change from baseline (p=0.23)

(b): Results confirmed using non-parametric test of 12 month values (p=0.47) and change from baseline (p=0.77)

(c): Results confirmed using non-parametric test of 12 month values (p=0.32) and change from baseline (p=0.55)

Table S6: Withdrawal from Treatment in Year 1 for those who commenced treatment (ITT population)

	Control (n=115)	Intervention (143)
Reason for withdrawal	0	26 (0)
No remission; patient decision	0	1 (3.8%)
Medical reasons	0	2 (7.7%)
Social reasons	0	8 (30.8%)
Limited weight loss	0	3 (11.5%)
Weight regain	0	1 (3.8%)
Other	0	6 (23.1%)
Not Known	0	5 (19.2%)

Table S7: Secondary outcomes: other binary outcomes in the intervention and control groups at 12 months

		N/Total (%)	Odds Ratio		
			Estimate	95% CI	p-value
	Control	121/148 (81.8%)			
Prescribed antihypertensive medications	Intervention	47/148 (31.8%)	0.30	(0.16, 0.54)	p=0.0001
	Control	91/148 (61.5%)			
Prescribed antidepressants	Intervention	40/148 (27.0%)	1.40	(0.79, 2.49)	p=0.2506
	Control	31/148 (20.9%)			
SBP >130mmHg	Intervention	67/128 (52.3%)	0.66	(0.37, 1.19)	p=0.1683
	Control	95/147 (64.6%)			
DBP >80mmHg	Intervention	80/128 (62.5%)	0.77	(0.46, 1.31)	p=0.3356
	Control	103/147 (70.1%)			

Intervention effects reported as estimated odds ratios (Intervention:Control), based on mixed effects logistic regression model, adjusted for randomised group, study centre (Tyneside, Scotland), and practice list size (≤5700, >5700) as fixed effects, and GP practice as a random effect.
Total N varies by outcome depending on data availability.

Table S8: Secondary outcomes: serum lipids in the intervention and control groups at baseline and 12 months

		N	Mean (SD)			Intervention Effect (Intervention:Control)			ICC
			Baseline	12months	Change	Estimate	95% CI	p-value	
Total cholesterol (mmol/l)	Intervention	121	4·3 (1·1)	4·5 (1·3)	0·23 (1·36)	1·03	(0·97, 1·10)	p=0·2874	0·05
	Control	147	4·3 (1·1)	4·3 (1·1)	0·07 (0·87)				
HDL-cholesterol (mmol/l)	Intervention	121	1·1 (0·3)	1·2 (0·4)	0·13 (0·25)	1·06	(1·00, 1·13)	p=0·0563	0·15
	Control	147	1·2 (0·3)	1·2 (0·3)	0·04 (0·21)				
Triglycerides (mmol/l)	Intervention	121	2·1 (1·4)	1·7 (1·4)	-0·31 (1·33)	0·80	(0·72, 0·89)	p<0·0001	<0·01
	Control	147	1·9 (0·9)	2·0 (1·2)	0·09 (0·92)				

Intervention effects reported as estimated relative differences (Intervention:Control), based on mixed effects linear regression model of log-transformed lipid measures, adjusted for randomised group, baseline value (log-transformed), 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 baseline and 12 months for each outcome. ICC: Intraclass Correlation Coefficient.

Table S9: Adverse effects identified a priori as relevant to the intervention treatment, experienced by intervention group participants during year one at study visits in each phase of the weight management programme. The usual-care control group was seen only at baseline and 12 months.

	TDR phase (12-20 weeks)				FR phase (2-8 weeks)				WLM phase (up to 52 weeks)			
	Total (n=139)	Mild	Moderate	Severe	Total (n=124)	Mild	Moderate	Severe	Total (n=94)	Mild	Moderate	Severe
Constipation	65 (46·8)	30 (21·6)	24 (17·3)	11 (7·9)	18 (14·5)	14 (11·3)	4 (3·2)	0 (0·0)	6 (6·4)	2 (2·1)	2 (2·1)	2 (2·1)
Sensitivity to cold	57 (41·0)	37 (26·6)	12 (8·6)	8 (5·8)	30 (24·2)	19 (15·3)	6 (4·8)	5 (4·0)	13 (13·8)	7 (7·4)	2 (2·1)	4 (4·3)
Headache	53 (38·1)	31 (22·3)	13 (9·4)	9 (6·5)	15 (12·1)	10 (8·1)	3 (2·4%)	2 (1·6)	8 (8·5)	5 (5·3)	2 (2·1)	1 (1·1)
Dizziness	49 (35·3)	40 (28·8)	7 (5·0)	2 (1·4)	11 (8·9)	3 (2·4)	6 (4·8)	2 (1·6)	7 (7·4)	4 (4·3)	3 (3·2)	0 (0·0)
Fatigue	45 (32·4)	24 (17·3)	11 (7·9)	10 (7·2)	18 (14·5)	10 (8·1)	3 (2·4)	5 (4·0)	8 (8·5)	2 (2·1)	0 (0·0)	6 (6·4)
Mood change	35 (25·2)	16 (11·5)	12 (8·6)	7 (5·0)	10 (8·1)	4 (3·2)	4 (3·2)	2 (1·6)	4 (4·3)	1 (1·1)	2 (2·1)	1 (1·1)
Nausea	25 (18·0)	15 (10·8)	4 (2·9)	6 (4·3)	3 (2·4)	3 (2·4)	0 (0·0)	0 (0·0)	1 (1·1)	1 (1·1)	0 (0·0)	0 (0·0)
Diarrhoea	23 (16·5)	11 (7·9)	10 (7·2)	2 (1·4)	5 (4·0)	4 (3·2)	1 (0·8)	0 (0·0)	1 (1·1)	1 (1·1)	0 (0·0)	0 (0·0)
Indigestion	20 (14·4)	15 (10·8)	3 (2·2)	2 (1·4)	4 (3·2)	2 (1·6)	2 (1·6)	0 (0·0)	1 (1·1)	1 (1·1)	0 (0·0)	0 (0·0)
Hair Loss	19 (13·7)	10 (7·2)	7 (5·0)	2 (1·4)	13 (10·5)	3 (2·4)	6 (4·8)	4 (3·2)	8 (8·5)	4 (4·3)	3 (3·2)	1 (1·1)

Data reported as N(%)

Table S10: Per-protocol analysis of primary outcomes

		N/Total (%)	Odds Ratio		
			Estimate	95% CI	p-value
Weight loss ≥15kg at 12 months	Intervention	36/128 (28·1%)	-	-	p<0·0001[(a)]
	Control	0/147 (0·0%)			
Diabetes remission (HbA_{1c} <48mmol/mol, off diabetic medication of ≥2 months)	Intervention	65/127[(b)] (51·2%)	23·8	(9·60, 58·8)	p<0·0001
	Control	6/147 (4·1%)			

Intervention effects reported as estimated odds ratios (Intervention:Control), based on mixed effects logistic regression model, adjusted for randomised group, study centre (Tyneside, Scotland), and practice list size (≤5700, >5700) as fixed effects, and GP practice as a random effect. For per protocol analyses, no assumptions were made about missing values.

(a) regression model could not be fitted for weight loss outcome; p-value from Fisher's Exact Test

(b) remission outcome missing for one subject in Intervention group due to blood sample not being obtained at 12 month visit, and no HbA_{1c} record being available in GP notes

Table S11: Subgroup analyses of primary outcomes: weight loss ≥15kg at 12 months. Given that none of the control group achieved this outcome, the planned analyses using logistic regression models with interaction terms were not possible, so the odds ratios presented here relate to achievement of the outcome in the Intervention group only, for each subgroup relative to the reference group

		Control	Intervention	Odds Ratio (within Intervention group)		
		N/Total (%)	N/Total (%)	Estimate	95% CI	p-value
Age at baseline (years)	<50	0/30 (0·0%)	9/52 (17·3%)	reference		
	50-54	0/31 (0·0%)	9/32 (28·1%)	1·78	(0·62, 5·17)	p=0·29
	55-59	0/31 (0·0%)	10/34 (29·4%)	2·14	(0·75, 6·07)	p=0·15
	≥60	0/57 (0·0%)	8/31 (25·8%)	1·64	(0·55, 4·86))	p=0·37
Sex	Male	0/93 (0·0%)	27/83 (32·5%)	reference		
	Female	0/56 (0·0%)	9/66 (13·6%)	0·32	(0·14, 0·76)	p=0·0094
Duration of diabetes (years)	<2	0/60 (0·0%)	6/50 (12·0%)	reference		
	≥2, <4	0/39 (0·0%)	13/47 (27·7%)	2·93	(1·00, 8·65)	p=0·051
	≥4, <6	0/50 (0·0%)	17/52 (32·7%)	3·82	(1·34, 10·85)	p=0·012
Baseline HbA_{1c} (%)	<7·0	0/50 (0·0%)	7/44 (15·9%)	reference		
	≥7·0, <8·0	0/66 (0·0%)	19/65 (29·2%)	2·10	(0·79, 5·60)	p=0·14
	≥8·0	0/33 (0·0%)	10/40 (25·0%)	1·92	(0·64, 5·77)	p=0·24
Baseline weight (kg)	<90	0/48 (0·0%)	3/40 (7·5%)	reference		
	≥90, <110	0/68 (0·0%)	18/71 (25·4%)	4·46	(1·21, 16·4)	p=0·024
	≥110	0/33 (0·0%)	15/38 (39·5%)	8·28	(2·13, 32·1)	p=0·0022
Number of oral anti-diabetic medications at baseline	None	0/34 (0·0%)	9/38 (23·7%)	reference		
	1	0/79 (0·0%)	14/65 (21·5%)	0·97	(0·36, 2·60)	p=0·96
	2+	0/36 (0·0%)	13/46 (28·3%)	1·37	(0·50, 3·73)	p=0·54

Estimated odds ratios based on mixed effects logistic regression model, adjusted for study centre (Tyneside, Scotland), and practice list size (≤5700, >5700) as fixed effects, and GP practice as a random effect.

Table S12: Subgroup analyses of primary outcomes: remission of diabetes (HbA_{1c} <48mmol/mol, off anti-diabetic medication for 2 months) at 12 months. Given that few in the control group achieved this outcome, the planned analyses using logistic regression models with interaction terms were highly underpowered, so the odds ratios presented here relate to achievement of the outcome in the Intervention group only, for each subgroup relative to the reference group

		Control	Intervention	Odds Ratio (within Intervention group)		
		N/Total (%)	N/Total (%)	Estimate	95% CI	p-value
Age at baseline (years)	<50	1/30 (3·3%)	17/52 (32·7%)	reference		
	50-54	1/31 (3·2%)	14/32 (43·8%)	1·53	(0·61, 3·83)	p=0·36
	55-59	1/31 (3·2%)	18/34 (52·9%)	2·47	(1·00, 6·09)	p=0·049
	≥60	3/57 (5·3%)	19/31 (61·3%)	3·27	(1·28, 8·31))	p=0·.013
Sex	Male	4/93 (4·3%)	27/83 (49·4%)	reference		
	Female	2/56 (3·6%)	9/66 (40·9%)	0·70	(0·36, 1·36)	p=0·29
Duration of diabetes (years)	<2	6/60 (10·0%)	22/50 (44·0%)	reference		
	≥2, <4	0/39 (0·0%)	24/47 (51·1%)	1·38	(0·61, 3·09)	p=0·44
	≥4, <6	0/50 (0·0%)	33/52 (42·3%)	0·97	(0·44, 2·13)	p=0·93
Baseline HbA_{1c} (%)	<7·0	5/50 (10·0%)	25/44 (56·8%)	reference		
	≥7·0, <8·0	1/66 (1·5%)	32/65 (49·2%)	0·68	(0·31, 1·53)	p=0·35
	≥8·0	0/33 (0·0%)	11/40 (27·5%)	0·28	(0·10, 0·73)	p=0·0099
Baseline weight (kg)	<90	3/48 (6·2%)	19/40 (47·5%)	reference		
	≥90, <110	1/68 (1·5%)	31/71 (43·7%)	2·10	(0·79, 5·60)	p=0·14
	≥110	2/33 (6·1%)	18/38 (47·4%)	1·92	(0·64, 5·77)	p=0·24
Number of oral anti-diabetic medications at baseline	None	6/34 (17·6%)	26/38 (68·4%)	reference		
	1	0/79 (0·0%)	30/65 (46·2%)	0·42	(0·18, 1·01)	p=0·053
	2+	0/36 (0·0%)	12/46 (26·1%)	0·17	(0·06, 0·45)	p=0·0004

Estimated odds ratios based on mixed effects logistic regression model, adjusted for study centre (Tyneside, Scotland), and practice list size (≤5700, >5700) as fixed effects, and GP practice as a random effect.