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Predictors of type 2 diabetes remission in the Diabetes Remission Clinical Trial (DiRECT)

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What's new?

- With ≥10 kg weight loss, 64% of early type 2 diabetes is reversible, but few data are available on factors predicting diabetes remission following diet-induced weight loss.
- Other than weight loss, most predictors were modest overall and, re-assuringly, none was sufficient to identify people for whom remission is not a worthwhile target.
- Remission was more likely for men, as a result of larger weight losses, and for those prescribed fewer antidiabetes medications at baseline. Remission was less likely for people with anxiety or depression, mainly due to smaller weight losses.
- Remission is a realistic aspiration for most people with type 2 diabetes diagnosed within 6 years, and achieving ≥10 kg weight loss should be a primary target of routine diabetes care at diagnosis, and before the escalation of therapy.

Abstract

Aim To identify predictors of type 2 diabetes remission in the intervention arm of DiRECT (Diabetes Remission Clinical Trial).

Methods Participants were aged 20–65 years, with type 2 diabetes duration of <6 years and BMI 27–45 kg/m^2, and were not receiving insulin. Weight loss was initiated by total diet

replacement (825–853 kcal/day, 3–5 months, shakes/soups), and weight loss maintenance support was provided for 2 years. Remissions [HbA_{1c} <48 mmol/mol (<6.5%), without antidiabetes medications] in the intervention group (n = 149, mean age 53 years, BMI 35 kg/m^2) were achieved by 68/149 participants (46%) at 12 months and by 53/149 participants (36%) at 24 months. Potential predictors were examined by logistic regression analyses, with adjustments for weight loss and effects independent of weight loss.

Results Baseline predictors of remission at 12 and 24 months included being prescribed fewer antidiabetes medications, having lower triglyceride and gamma-glutamyl transferase levels, and reporting better quality of life with less anxiety/depression. Lower baseline HbA_{1c} was a predictor at 12 months, and older age and male sex were predictors at 24 months. Being prescribed antidepressants predicted non-remission. Some, but not all effects were explained by weight loss. Weight loss was the strongest predictor of remission at 12 months (adjusted odds ratio per kg weight loss 1.24, 95% CI 1.14, 1.34; P < 0.0001) and 24 months (adjusted odds ratio 1.23, 95% CI 1.13, 1.35; P <0.0001). Weight loss in kilograms and percentage weight loss were equally good predictors. Early weight loss and higher programme attendance predicted more remissions. Baseline BMI, fasting insulin, fasting C-peptide and diabetes duration did not predict remission.

Conclusions Other than weight loss, most predictors were modest, and not sufficient to identify subgroups for which remission was not a worthwhile target.

Introduction

Type 2 diabetes has traditionally been viewed as a progressive, irreversible condition; however, remission is high on the agenda of people with diabetes [1], and the concept is increasingly recognized within clinical guidelines [2]. We showed within a primary care-based randomized controlled trial that a large proportion of people living with type 2 diabetes

can achieve sustained remissions if they lose sufficient weight within 6 years of diagnosis [3, 4]. Potentially life-changing remissions were clearly related to degree of weight loss, at 1 year reaching 73% with ≥10-kg loss, and 86% with ≥15-kg loss. Intensive weight management programmes place new demands on people seeking remission and on healthcare services, so there could be value in identifying individuals or subgroups who are more likely to achieve remission, or for whom weight loss is likely to be unsuccessful. However, little published evidence allows prediction of diabetes remission following diet-induced weight loss. We have therefore conducted a *post hoc* analysis of demographic and clinical data in the DiRECT (Diabetes Remission Clinical Trial) database to investigate whether it is possible at baseline or early in treatment to predict which people are more or less likely to achieve remission, with reference to factors also predicting weight loss.

Methods

DiRECT is a cluster-randomized, clinical trial, conducted within routine primary care practice. The study protocol [5], recruitment and baseline data [6] and primary outcome results have all been published [3,4]. The trial was registered at Controlled Trials, www.controlled-trials.com/ISRCTN03267836. Practices agreeing to participate were randomized to intervention or control arms, which proved well balanced at baseline with regard to demographic and clinical factors [6]. The main inclusion criteria were type 2 diabetes, diagnosed using WHO criteria, within 6 years, with most recent HbA_{1c} ≥48 mmol/mol [≤6.5%; or ≥43 mmol/mol (≤6.1%) if on antidiabetes medication], age 20–65 years and BMI 27–45 kg/m^2. Given that weight loss is the main determinant of remission, our analyses were restricted to the intervention group in DiRECT, although a few controls did achieve remission (n = 6 at 12 months, n = 5 at 24 months).

The intervention was an evidence-based weight management programme [7], delivered in participants' own general practice by a practice nurse or local dietitian. Briefly, weight loss was initiated by 12–20 weeks of total diet replacement (825–853 kcal/day, shakes/soups) and fortnightly study visits, followed by food reintroduction, and monthly support for long-term weight loss maintenance up to 2 years. All oral antidiabetes and anti-hypertensive drugs were discontinued on commencing the weight management programme. Blood glucose and blood pressure were monitored at each appointment, and medications were reintroduced if indicated.

Outcomes

Baseline factors and weight losses during the intervention period were examined as potential predictors of remission at 12 and 24 months in the intervention group (n = 149, mean age 53 years, BMI 35 kg/m^2). Remission was defined as HbA_{1c} <48 mmol/mol (<6.5%), after at least 2 months without glucose-lowering medications, in line with criteria adopted by UK and other diabetes organizations [8,9]. Predictor variables were selected based on available data within the DiRECT database. Data were collected at baseline, 12 and 24 months, or from general practice records (if available within a window of ±100 days), as prespecified in the protocol for participants who ceased to engage and did not attend their 12- and 24-month trial appointment [5]. For those participants who did not attend the 12- and 24-month study assessments, and for whom data could not be obtained from general practice records, we made the assumption that remission was not achieved. Weight change data were available for 137 participants at 12 months, and 129 participants at 24 months.

Statistical analysis

Continuous variables are summarized as mean and standard deviation, as all were deemed sufficiently normally distributed. Categorical variables are summarized as number and percentage per category. To assess the effect of baseline characteristics on remission, mixed

effects logistic regression was used. It is assumed that the main effect of the intervention is weight loss. We also examined whether factors other than weight loss may be predictors of remission. In trying to separate these effects we analysed the relation of weight loss to remission using a mixed effects logistic regression model predicting remission from weight loss. The residuals of this model represent the part of the remission information that is not explained by weight loss. In the next step, for each baseline characteristic, we have fitted a linear mixed effects regression model predicting the residuals from the first model, i.e. the part of remission that is not explained by weight loss. In addition, for each baseline characteristic, we fitted a linear mixed effects regression model predicting weight loss from the baseline characteristic. All analysis models were adjusted for the stratification variables used in the randomization [study centre (Scotland or Tyneside), practice list size (≤5700, >5700)] and a random effect for practice. Statistical analyses were carried out in R for Windows, version 3.2.4. A 5% α-level was used throughout, with no adjustment for multiplicity of statistical tests.

Ethics

Ethical approval was granted from the West of Scotland Research Ethics Committee (reference number: 13/WS/0314) and all participants provided written informed consent.

Results

Baseline characteristics have been reported previously [3,4,6] and additional details for the 149 participants in the intervention arm are shown in Table 1. The study drop-out rate was low, and predictors of diabetes remission were derived using available data from 142/149 participants (95%) at 12 months, and 129/149 participants (87%) at 24 months.

Predictors of type 2 diabetes remission at 12 and 24 months

Remission of type 2 diabetes was achieved by 46% (*n*=68/149) of participants at 12 months, and by 36% (*n*=53/149) at 24 months.

Baseline predictors of remission

Single and multivariate model predictors of remission are shown in Figs 1 and 2, with the effect of weight loss and effects independent of weight loss for each predictor variable also shown (additional remission predictor data are available in Appendix S1). Being prescribed fewer antidiabetes medications was the strongest predictor at 12 and 24 months (P<0.001), an effect confirmed by multivariate analysis, and odds of remission were lowest for those prescribed sulfonylureas and metformin. Participants with higher HbA_{1c} were less likely to achieve remission at 12 months [adjusted odds ratio per 1 mmol/mol: 0.96 (0.93, 0.99), P=0.017; adjusted odds ratio per 1%: 0.66 [0.47, 0.93], P=0.018], although the effects were attenuated by 24 months [adjusted odds ratio per 1 mmol/mol: 0.97 (0.94, 1.00), P=0.062; adjusted odds ratio per 1%: 0.71 (0.50, 1.02), P=0.062]. Odds of remission were also lower at 12 and 24 months for participants with higher triglyceride and gamma-glutamyl transferase (GGT) concentrations, and GGT was a predictor in the 24-month multivariate model [adjusted odds ratio per 1 units/l, 0.99 (0.97, 1.00); P=0.022]. Higher systolic blood pressure was a predictor of remission at 12 and 24 months (single and multivariate models) and increasing age predicted remission at 24 months only.

Better quality of life [as measured by the EuroQol five-dimension questionnaire (EQ-5D) score] and no problems with pain were predictors of remission across the study and neither were explained by weight loss effects, whereas higher levels of anxiety/depression and antidepressant usage predicted non-remission, largely due to smaller weight losses. Deprivation category (Index of Multiple Deprivation), when considered as a whole,

influenced remission [12 months: *P*=0.020 (multivariate model only); 24 months: *P*=0.049 (single predictor model only)], although statistical differences between subgroups were not observed. Quality-of-life scores were higher for people in more affluent groups (*P* = 0.004), but deprivation did not explain anti-depressant usage (*P* = 0.946).

There was no statistically significant sex effect on remission at 12 months, but remissions were more durable in men, with significant differences evident at 24 months, effects which were explained by greater absolute weight loss. Men had greater weight losses than women at 12 months [11.7 ± 7.8 kg/11.0 ± 6.7% vs 7.8 ± 7.8 kg/8.4 ± 5.6%; *P*=0.004 (kg), *P*=0.067 (%)] and 24 months [8.9 ± 6.3 kg/8.5 ± 8.4% vs 6.0 ± 6.4 kg/6.6 ± 7.0%; *P*=0.012 (kg), *P*=0.136 (%)]. Being prescribed antidepressants was associated with significantly less weight loss throughout the study, and was a predictor of non-remission at 24 months. Fasting insulin, fasting C-peptide and duration of diabetes were not predictors of remission at either time point.

Programme-related predictors of remission

Figure 3 shows remission rates by weight loss category from baseline in intervention group participants. Weight loss was the strongest predictor of remission at 12 and 24 months, irrespective of baseline BMI, with absolute (kg) and percentage (%) weight loss equally good predictors. Numbers of remissions increased in a stepwise manner with weight loss (Fig. 3). Weight losses achieved as early as 4 weeks were significant predictors of remission at 12 and 24 months, and higher programme attendance was also associated with achieving remission. Of the 68 participants achieving initial remission at 12 months, 29% (20/68) relapsed and diabetes re-occurred at 24 months. Average weight regain was 7.1 ± 5.4 kg in relapsers compared to 4.2 ± 3.7 kg in those maintaining remission (*P*=0.073).

Protocol for early stopping of treatment

At 8 weeks, 28 participants (19%) had failed to achieve 6-kg weight loss, but six of the 28 did not start the total diet replacement intervention after enrolment. Of the remaining 22 participants, 11 withdrew from treatment before the end of the total diet replacement phase and six participants went on to achieve remission (89% sensitivity, 23% specificity for predicting remission at 24 months).

Discussion

An ability to predict treatment success, or failure, from baseline information might be of value to manage the expectations of people who currently have type 2 diabetes, and clinicians, and also to guide resource management. In this *post hoc* analysis of the DiRECT trial, we found several baseline measures which were statistical predictors of remission, some of which were not explained by differences in weight loss; however, predictive power was modest at best, and in practice none was sufficient to identify people for whom remission was not a worthwhile goal. Remission should therefore be considered a realistic management target for any individual within 6 years of diagnosis. It can be achieved safely and effectively using evidence-based weight management [10,11], and most individuals will achieve remission with ≥10 kg/% weight loss, although ≥15kg/% provides greater assurance.

This paper attempts to answer some of the most common practical questions being asked by clinicians and healthcare planners regarding likelihood of remission, and was therefore restricted to examining possible predictors of practical clinical value, rather than addressing mechanistic predictors. The strongest baseline predictor of remission related to antidiabetes medications prescribed, with greater likelihood of remission when weight loss is achieved prior to the introduction of first- or second-line oral hypoglycaemic agents. Reverse causality is possible, since being prescribed more medications is likely to be a marker of disease

progression and declining β-cell function, obstructing remission. After diagnosis, the step between intensifying antidiabetes drug therapy, from one agent to two, represents an important signal that the opportunity for remission is diminishing. We identified several predictors of remission, and effect sizes for many of these appear reasonably strong, but confidence intervals are fairly wide, suggesting the precision and certainty of these estimates are too weak to have reliable clinical relevance, or to justify influence over policy or resource allocation. Reassuringly, remissions remained frequent across these variables, and some predictors (e.g. male sex, less anxiety/depression) were explained by greater weight loss. Although not all people with type 2 diabetes are able to achieve remission, limiting this type of service to those most likely to be successful cannot be done using the criteria examined. The predictive ability of a multivariate score was also limited, and was insufficient for use in clinical practice without disadvantaging large numbers (Table S5).

Perhaps unexpectedly, diabetes duration, and fasting insulin and C-peptide concentrations did not emerge as significant predictors of remission, probably because DiRECT only included participants within 6 years of diagnosis, although, a modest benefit for shorter disease duration was observed in a subgroup of participants reported separately [14]. Previous studies found that diabetes duration >6 years does impede remission [12,13] and shorter history of type 2 diabetes and higher C-peptide levels are consistent predictors of remission after bariatric surgery [14]. Remissions were less likely for participants with elevated triglyceride and GGT concentrations: both are associated with non-alcoholic fatty liver disease [15], commonly coexisting with type 2 diabetes, and are likely to reflect more extensive hepatic damage. People with a history of alcohol misuse were excluded from DiRECT, but we cannot exclude additional effects from alcohol. Older age and higher blood pressure both emerged as modest predictors of remission, associations which are counter-intuitive and require confirmation in future studies. There are some parallels between these results and data from

the Look AHEAD trial, which reported 12% remissions with a mean 8-kg weight-loss at 12 months, as a *post hoc* finding in participants with substantially longer-standing diabetes than in DiRECT. Remissions were more frequent among participants with greater weight loss at 12 months, shorter histories of diabetes, lower baseline HbA_{1c}, and in those not using insulin or taking anti-hypertensive drugs. Although the DiRECT study excluded people treated with insulin, this is unlikely to have introduced any unusual heterogeneity or bias, because relatively few people are on insulin therapy within 6 years of type 2 diabetes diagnosis.

There was a weak relationship between remission and the deprivation variable when considered as a whole, and our findings indicate that people living in more socially deprived areas were less likely to achieve remission (Figs 1 and 2). This effect may have been related to other factors, such as lower quality of life, which was associated with higher deprivation and non-remission. These factors may warrant investigation in future studies.

Weight loss is by far the most potent predictor of remission, which raises questions regarding predictors of weight loss, and also weight loss maintenance. Success or failure in losing and maintaining weight is influenced by interacting biological, behavioural and environmental factors, and identifying reliable predictors in previous studies has proved difficult [16,17]. Although it is beyond the scope of the present study to include a detailed investigation of weight loss predictors, the predictors of remission which were explained by weight change must themselves be predictors of weight loss and maintenance. For example, higher anxiety/depression scores and antidepressant drug usage predicted poorer weight loss and therefore worse remission outcomes. Many antidepressant medications are obesogenic [18], and persisting negative mood states are likely to interfere with adhering to diet and lifestyle recommendations for weight loss maintenance [19]. More remissions at 24 months in men was also explained principally by greater weight loss. The greater (absolute) weight loss in men was expected, since the fixed-energy diet prescribed during the initial weight loss period

created a greater energy deficit in males, but higher percentage weight loss observed at both 12 and 24 months implies that, in this context, men are particularly capable of adhering to a restrictive, low-calorie intervention. Men exhibit earlier and greater ectopic fat accumulation, whereas women have larger stores of safer subcutaneous fat [20]. Given their greater initial intra-abdominal fat stores, men are likely to have mobilized more visceral and less subcutaneous fat than women, contributing greater improvements in insulin sensitivity. Although fewer men than women tend to enrol onto weight management programmes [21], 59% enrolled into DiRECT (with 56% in the intervention arm), suggesting that men were motivated by the potential of remission, discontinuing medications and overall health improvement. Frequency of professional contacts in clinical weight management trials is a consistent predictor of programme adherence and weight loss and maintenance [16]. Whether attendance predicts weight loss/remission, the reverse, or both relationships, is unclear. Reverse causality may play a part since individuals regaining the most weight, and thus at greatest risk of remission relapse, are less likely to attend programme appointments, whereas success enhances motivation and promotes engagement.

It is notable that weight loss achieved in the early weeks of treatment (by 4 weeks) was associated with remission status at 12 and 24 months. This confirms that those losing weight most rapidly achieve better long-term outcomes [22]. Early weight loss on a low-calorie diet is a clear marker of intervention acceptability and adherence, such that early 'stopping rules' could be proposed, to exclude those who fail to achieve pre-specified early weight loss targets, however, in practice, we found that many who failed to achieve early weight loss withdrew from treatment of their own accord, and others still go on to be successful. Based on the DiRECT results, withdrawing the intervention from people who did not have good early weight loss would deny effective treatment to a significant minority who benefit from continued support and go on to achieve remissions at 12 and 24 months.

Durability of remission is dependent on weight loss maintenance, with remission relapsers regaining more weight between 12 and 24 months compared to those remaining in remission. In DiRECT participants achieving remission but subsequently relapsing, weight regain was strongly associated with re-accumulation of ectopic fat within the liver and pancreas [23]. These findings are consistent with the view that both onset, and remission, of type 2 diabetes is determined by exceeding, or getting below, a 'personal fat threshold' within the liver and pancreas [24]. There is a common belief that complete weight regain following diet-induced weight loss is inevitable, because of physiological adaptations [25] and environmental influences [26] opposing long-term weight loss maintenance; however, in DiRECT, a mean weight loss of 11.4 kg (>10% body weight) in those achieving remission (*n*=53) at 2 years adds to the evidence that failure is not inevitable [27,28].

While DiRECT offers a unique opportunity to assess potential clinical and demographic predictors of remission of type 2 diabetes, with a relatively large and complete database of robust measurements, an even larger sample size would have provided further assurances with regard to the conclusions of our analyses. The study was conducted in people with a relatively short duration diabetes, and predominantly in white Europeans. More evidence is needed to establish the likelihood of remission with similar weight losses for people with longer disease durations, including those treated with insulin, and in people of other ethnicities, although in a study similar to DiRECT, even higher remission rates were documented in a younger population from the Middle East/North Africa with shorter average (<2 years) history of diabetes [29].

In conclusion, remissions were frequent across all variables examined. The strongest predictors were greater weight loss and being prescribed fewer antidiabetes medications at baseline, whilst disease duration, fasting insulin and C-peptide did not influence likelihood of remission. Men were more successful at sustaining remission and weight losses over time,

and appear well suited to this intervention. People with anxiety and/or depression were less successful and may benefit from additional support in weight management interventions. Other predictors of type 2 diabetes remission were modest, were largely explained by greater weight loss, and none was sufficient to identify people for whom remission is not a worthwhile target. These findings provide reliable and reassuring evidence to clinicians, healthcare planners and people targeting type 2 diabetes remission.

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Competing interests

M.E.J.L. reports personal fees from Roche, Novo Nordisk and Eli Lilly. L.M. reports personal fees from Counterweight Ltd and Cambridge Weight Plan. W.S.L. and G.T. report personal fees from Cambridge Weight Plan. R.T. reports lecture fees from Lilly and Novartis, and consultancy fees from Wilmington Healthcare. A.C.B. reports personal fees from Novo Nordisk, Napp Pharmaceuticals and Eli Lilly. N.B. reports personal fees from Counterweight Ltd, Cambridge Weight Plan and the British Dietetic Association. N.S. reports personal fees from Amgen, AstraZeneca, Eli Lilly, NAPP Pharmaceuticals, Novo Nordisk, Pfizer and Sanofi, and grants and personal fees from Boehringer Ingelheim, outside the submitted work. All other authors report no conflict of interest.

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References

1. 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; **5**: 935–936.

2. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G *et al.* Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2018; **61:** 2461–2498.

3. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L *et al*. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018; **391**: 541–551.

4. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L *et al.* Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019; **7**: 344–355.

5. Leslie WS, Ford I, Sattar N, Hollingsworth KG, Adamson A, Sniehotta FF *et al*. The Diabetes Remission Clinical Trial (DiRECT): protocol for a cluster randomised trial. *BMC Fam Pract* 2016; **17**: 20.

6. Taylor R, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L *et al.* Clinical and metabolic features of the randomised controlled Diabetes Remission Clinical Trial (DiRECT) cohort. *Diabetologia* 2018; **61**: 589–598.

7. McCombie L, Brosnahan N, Ross H, Bell-Higgs A, Govan L, Lean M. Filling the intervention gap: service evaluation of an intensive nonsurgical weight management programme for severe and complex obesity. *J Hum Nutr Diet* 2018; **32**: 329–337.

8. Nagi D, Hambling C, Taylor R. Remission of type 2 diabetes: a position statement from the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS). *Br J Diabetes* 2019; **19**: 73–76.

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

10. Hopkins MD, Taylor R, Lean MEJ. The DiRECT principles: giving Type 2 diabetes remission programmes the best chance of success. *Diabet Med* 2019; 36:1703-1704.

11. Baldry EL, Davies MJ, Khunti K, Webb DR. Pragmatic management of low-energy diets in people with type 2 diabetes in primary care: a decision aid for clinicians. *Diabet Med* 2020; **37**: 747–751.

12. Steven S, Hollingsworth KG, Al-Mrabeh A, Avery L, Aribisala B, Caslake M *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**: 808–815.

13. 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* 2012; **308**: 2489–2496.

14. Dixon JB, Chuang L-M, Chong K, Chen S-C, Lambert GW, Straznicky NE *et al.* Predicting the Glycemic Response to Gastric Bypass Surgery in Patients With Type 2 Diabetes. *Diabetes Care* 2013; **36**: 20–26.

15. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A *et al.* The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006; **6**:33.

16. Stubbs J, Whybrow S, Teixeira P, Blundell J, Lawton C, Westenhoefer J *et al.* Problems in identifying predictors and correlates of weight loss and maintenance: implications for weight control therapies based on behaviour change. *Obes Rev* 2011; **12**: 688–708.

17. Carraca EV, Santos I, Mata J, Teixeira PJ. Psychosocial Pretreatment Predictors of Weight Control: A Systematic Review Update. *Obesity Facts* 2018; **11**: 67–82.

18. Leslie WS, Hankey CR, Lean MEJ. Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review. *QJM* 2007; **100**: 395–404.

19. Fabricatore AN, Wadden TA, Moore RH, Butryn ML, Heymsfield SB, Nguyen AM. Predictors of attrition and weight loss success: Results from a randomized controlled trial. *Behav Res Ther* 2009; **47**: 685–691.

20. Sattar N. Gender aspects in type 2 diabetes mellitus and cardiometabolic risk. *Best Pract Res Clin Endocrinol Metab* 2013; **27**: 501–507.

21. Robertson C, Avenell A, Boachie C, Stewart F, Archibald D, Douglas F *et al.* Should weight loss and maintenance programmes be designed differently for men? A systematic review of long-term randomised controlled trials presenting data for men and women: The ROMEO project. *Obes Res Clin Pract* 2016; **10:** 70–84.

22. Nackers LM, Ross KM, Perri MG. The Association Between Rate of Initial Weight Loss and Long-Term Success in Obesity Treatment: Does Slow and Steady Win the Race? *Int J Behav Med* 2010; **17**: 161–167.

23. Al-Mrabeh A, Zhyzhneuskaya SV, Peters C, Barnes AC, Melhem S, Jesuthasan A *et al.* Hepatic Lipoprotein Export and Remission of Human Type 2 Diabetes after Weight Loss. *Cell Metab* 2020; **31**: 233–249.

24. Taylor R, Holman RR. Normal weight individuals who develop Type 2 diabetes: the personal fat threshold. *Clin Sci* 2015; **128**: 405–410.

25. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A *et al.* Long-Term Persistence of Hormonal Adaptations to Weight Loss. *NEJM* 2011; **365**: 1597–1604.

26. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML *et al.* The global obesity pandemic: shaped by global drivers and local environments. *Lancet* 2011; **378**: 804–814.

27. Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. Weight-Loss Maintenance for 10 Years in the National Weight Control Registry. *Am J Prev Med* 2014; **46**: 17–23.

28. Kraschnewski JL, Boan J, Esposito J, Sherwood NE, Lehman EB, Kephart DK *et al.* Long-term weight loss maintenance in the United States. *Int J Obes* 2010; **34**: 1644–1654.

29. Taheri S, Zaghloul H, Chagoury O, Elhadad S, Ahmed SH, El Khatib N *et al.* Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an

open-label, parallel-group, randomised controlled trial. *Lancet Diabetes Endocrinol* 2020; **8**: 477–489.

30. Bruce B, Wilfley D. Binge eating among the overweight population: A serious and prevalent problem. *J Am Diet Assoc* 1996; **96**: 58–61.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1

Table S1 Predictions of remission at year 1 from baseline characteristics and from weight losses and attendance during the programme. Baseline predictors of remission take into account the estimated effect of weight loss and effects independent from weight loss.

Table S2 Predictors of remission at year 2 from baseline characteristics, weight losses and attendance during the programme. Baseline predictors of remission take into account the estimated effect of weight loss and effects independent from weight loss.

Table S3 Multivariate analysis of baseline characteristics and early weight loss in predicting remission at year 1 taking into account the estimated effect of weight loss and effects independent from weight loss.

Table S4 Multivariate analysis of baseline characteristics and early weight loss in predicting remission at year 2 taking into account the estimated effect of weight loss and effects independent from weight loss.

Table S5 Multivariate predictor scores of remission at year 1 and 2 from all potential predictors using the lasso method.

Table 1 Baseline characteristics of the intervention group, by remission status at 12 and 24 months

	All (*n*=149)	**No remission at 12 months or 24 months (*n*=76)**	**Remission at 12 months but not 24 months (*n*=20)**	**Remission at 24 months (*n*=53)**
Age, years	52.9 (7.6)	51.5 (7.8)	51.2 (7.7)	55.6 (6.6)
Men, *n* (%)	83 (56)	39 (51)	7 (35)	37 (70)
Women, *n* (%)	66 (44)	37 (49)	13 (65)	16 (30)
IMD, *n* (%)				
Quintile 1 – most deprived	31 (21)	19 (25)	4 (24)	8 (15)
Quintile 2	24 (16)	14 (18)	3 (18)	7 (13)
Quintile 3	38 (26)	23 (30)	4 (24)	11 (21)
Quintile 4	29 (20)	10 (13)	5 (29)	14 (26)
Quintile 5 – least deprived	24 (16)	10 (13)	1 (6)	13 (25)
Diabetes duration, years	3.0 (1.7)	3.1 (1.8)	3.0 (1.8)	3.0 (1.5)
Weight, kg	101.0 (16.7)	101.1 (17.5)	101.1 (18.5)	100.9 (15.1)
BMI, kg/m^2	35.1 (4.5)	34.9 (4.6)	36.6 (3.7)	34.8 (4.7)
Systolic blood pressure, mmHg	132.7 (17.5)	129.5 (16.1)	134.4 (20.5)	136.6 (17.6)
EQ-5D health utility score	0.8 (0.3)	0.7 (0.3)	0.9 (0.1)	0.9 (0.2)
EQ-5D Mobility, number with problems (%)	40 (27)	27 (36)	4 (20)	9 (17)
EQ-5D Selfcare, number with problems (%)	14 (9)	10 (13)	1 (5)	3 (6)
EQ-5D Activities, number with problems (%)	34 (23)	23 (30)	4 (20)	7 (13)
EQ-5D Pain, number with problems (%)	63 (42)	40 (53)	7 (35)	16 (30)
EQ-5D Anxiety and depression, number with problems (%)	37 (25)	28 (37)	6 (30)	3 (6)
EQ-5D 100-point visual analogue scale	65.8 (19.1)	62.9 (19.6)	57.4 (13.8)	73.1 (18.1)
HbA_{1c}, mmol/mol	60.4 (13.7)	63.4 (14.6)	58.2 (15.0)	57.0 (10.7)

HbA_{1c}, %	7.7 (1.3)	8.0 (1.3)	7.5 (1.4)	7.4 (1.0)
Insulin, µUml	24.5 (15.0)	23.9 (14.1)	25.7 (12.4)	25.1 (17.0)
C-peptide, ng/ml	5.4 (2.4)	5.6 (2.4)	5.7 (2.2)	5.2 (2.5)
Gamma-glutamyl transferase, units/l	50.2 (51.0)	56.0 (65.8)	48.4 (25.1)	42.4 (28.3)
Triglycerides, mmol/l	2.1 (1.4)	2.2 (1.4)	1.6 (0.6)	2.0 (1.5)
Number of antidiabetes medications	1.1 (0.9)	1.5 (1.0)	0.9 (0.8)	0.8 (0.7)
Not prescribed metformin or gliclazide, *n* (%)	38 (26)	12 (16)	6 (30)	20 (38)
Metformin only, *n* (%)	75 (50)	37 (49)	12 (60)	26 (49)
Gliclazide only, *n* (%)	8 (5)	5 (6)	0 (0)	3 (6)
Metformin and gliclazide, *n* (%)	28 (19)	22 (29)	2 (10)	4 (8)
Number of anti-hypertensive medications	1.0 (1.2)	0.9 (1.1)	1.1 (1.0)	1.2 (1.2)
Prescribed antidepressants, *n* (%)				
No	109 (73)	49 (65)	12 (60)	48 (91)
Yes	40 (27)	27 (35)	8 (40)	5 (9)
Binge eating score (min. = 0, max. = 4)	1.3 (1.3)	1.4 (1.5)	1.5 (1.3)	1.2 (1.2)

EQ-5D, EuroQol five-dimension questionnaire; IMD, Index of Multiple Deprivation.

Data are presented as mean± SD, unless otherwise stated.

IMD was assessed according to study participant postcode, binge eating scores were determined using a simple screening questionnaire [30] and quality of life was measured by the EQ-5D.