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Brief formula low-energy-diet for relapse management during weight loss maintenance in the Diabetes Remission Clinical Trial (DiRECT)

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Abstract

Background: Weight loss maintenance (WLM) is critical for sustaining type 2 diabetes (T2D) remission, but poorly evidenced. We evaluated brief return to formula low-energy-diet (LED) as relapse treatments (RTs) during the WLM phase of the Diabetes Remission Clinical Trial (DiRECT).
Methods: This post-hoc evaluation included all participants commencing the WLM phase of DiRECT. The protocol offered RT when regain of >2 kg occurred.
Results: In total, 123/149 (83%) DiRECT intervention participants commenced the WLM phase after 26 (17%) had withdrawn prior to the WLM phase. Most participants [99/123 (80%)] regained >2 kg during the WLM phase, among whom 60/99 (61%) were recorded as using RT and 39/99 (39%) not using any RT. At baseline, RT users had a higher mean (SD) body mass index [35.8 (4.9) kg m^{-2} vs. 33.8 (3.9) kg m^{-2}, $p = 0.0231$] and had greater social deprivation ($P = 0.0003$) than non-users, although otherwise the groups were similar. Weight loss ≥ 2k g was achieved in 30/93 (32%) of RT attempts. At 2 years, those regaining >2 kg and using RT ($n = 60$) had mean (SD) weight losses of 7.4 (6.1) kg, with 25 (42%) remissions and 7 (12%) programme withdrawals. Those regaining >2 kg but not using RT

(*n* = 39) had weight losses of 8.8 (6.0) kg, with 21 (54%) remissions and 4 (10%) programme withdrawals (all not significant). Twelve participants were never recorded as having regained >2 kg or using RTs and, at 2 years, their weight losses were 12.9 (9.2) kg, with 4 (33%) remissions and 8 (67%) programme withdrawals.
Conclusions: Most people with T2D experience weight regain >2 kg during the 2 years after substantial weight loss with a LED. Only one-third of RTs corrected their 2-kg regain, resulting in similar weight losses, remissions and programme withdrawals at 2 years compared to those not using RTs; however, both groups had weight losses below those not recorded as regaining >2 kg during WLM.

Introduction

The Diabetes Remission Clinical Trial (DiRECT) demonstrated that a weight management programme including total diet replacement (TDR) with integrated food reintroduction (FR) and weight loss maintenance (WLM) sustained sufficient weight losses for type 2 diabetes (T2D) remission in almost half the participants.[1-3] Remission is now a recognised treatment target for people with T2D,[4] and remission services are currently being established.[5, 6]
In DiRECT, 53/149 maintained remission by 2 years, achieving mean (SD) weight losses of 10.4 (6.8) kg. However, 17/149 achieved remission at 1 year but not 2 years and had regained to leave weight losses of only 3.7 (5.9) kg.[3] Delaying or minimising regain is therefore critical, following intentional weight loss, to sustain remissions, as well as optimise metabolic health and quality of life,[7] although it is the major challenge for people with obesity, a chronic, relapsing condition.[8]
Weight regain is the result of complex interactions between biology, environment and behaviours.[9, 10] Although so frequent as to be expected as usual, it is rarely addressed proactively by health professionals or people living with obesity, and it has attracted far too little research.[9, 11, 12] Proactive relapse training for anticipated lapses or relapses usually focus on self-monitoring of behaviours and goal setting with reinforcement of the original weight loss strategy, which may not be so appropriate for WLM: different or more intensive approaches may be necessary to overcome the complex reasons for weight regain.[9, 13-15] One relapse treatment (RT) approach is to offer brief intensive periods of formula low-energy-diet (LED) when weight increases above a defined cut-off point. To our knowledge, this RT approach has not been studied before in people with T2D in a primary care setting.
In the Counterweight-Plus feasibility study, undertaken prior to DiRECT, 17/52 (33%) participants starting WLM requested a brief return to LED to assist WLM.[16] Therefore, using continuous improvement methodology, RTs were included as a preplanned component of DiRECT.[1, 17] RTs aim to correct small (2–4 kg) regains promptly, as well as limit or minimise long-term weight regain.[14] This post-hoc evaluation reports weight losses, remissions and programme withdrawals at 2 years for those eligible for, and using or not using RTs, during the WLM phase of DiRECT.

Materials and Methods

Study Design and participants

A detailed description of DiRECT, including the main study results, has been published elsewhere.[1-3] Briefly, DiRECT was a 2-year open label cluster-randomised controlled trial, conducted in 49 primary care sites across Scotland and England.[1] The

trial was designed to assess an intensive weight management programme to achieve weight loss and T2D remission compared to standard guideline care. Co-primary endpoints were weight reduction ≥15 kg and HbA_{1c} <48 mmol mol^{-1} (off anti-diabetes medications) at 1 year, with further WLM support up to 2 years.[1] Participation was open to men and women with T2D (duration 0–6 years, not requiring insulin), aged 20–65 years, with body mass index (BMI) 27–45 kg m^{-2} and no medical exclusions.[1] DiRECT is listed with the ISRCTN registry (number 03267836).[1] Ethical approval was granted by West 3 Ethics Committee on the 24 January 2014 (reference number: 13/WS/0314).[1-3] Subsequent approvals were provided by the National Health Service (NHS) areas in Scotland and clinical commissioning groups in the Tyneside region of England.[1-3] All participants provided their written informed consent.[1-3]

Intervention

The DiRECT intervention has been described in detail previously.[1, 16, 18] In brief, the weight management programme aimed for ≥ 15 kg weight loss using TDR (825–853 kcal day^{-1} LED) 3–5 months, followed by stepped FR for 1–2 months and WLM support for approximately 18 months. All anti-hypertensive and anti-diabetic medications were discontinued on day 1 of TDR. During WLM, participants were offered monthly appointments (approximately 30 min) with practice nurses/dietitians and, using a goal setting approach participants, were supported to maintain dietary, physical activity and behavioural changes adopted during the TDR and FR phases. Weight, blood pressure and capillary blood glucose were measured at all appointments using standardised procedures.[1]

Relapse treatments

Throughout the WLM phase, regular self-monitoring of weight was recommended, aiming to keep weight within 2 kg of their achieved weight (allowing for normal body weight variation and to ensure regain was treated promptly).[1, 14, 19] RTs were optional and offered if regain was >2 kg: 4 weeks FR and/or orlistat. The FR RT was a partial-meal-replacement (increasing from 1000 kcal to 1400 kcal over 4 weeks) and including one or two formula products. This RT included two fortnightly practitioner appointments and 42 formula products. If regain was >4 kg: 4 weeks TDR. RT TDR contained 825–853 kcal day^{-1}, and included two to four practitioner appointments (depending on participants needs) and 112 formula products. Thereafter, participants moved onto FR as described above.[1] On completion of the RT, participants continued on the WLM protocol.

Analysis

Data collection procedures are described elsewhere.[1] This post-hoc analysis included participants commencing the WLM phase of DiRECT who had follow-up data available at 2 years. Data are presented for those regaining >2 kg because similar outcomes were observed for those regaining 2–4 kg and >4 kg. The other specific criteria which could trigger RT TDR according to the DiRECT protocol (regain to <15 kg below starting weight or HbA_{1c} increase to above 48 mmol mol^{-1}), if used, were not recorded in the dataset. The reasons why participants chose to use or not use RT or orlistat were not recorded in the dataset.

An intention-to-treat analysis compared those regaining >2 kg and recorded as using or not using RTs. Weight losses, remissions (HbA_{1c} <48 mmol mol^{-1} off all anti-diabetic agents) and programme withdrawals at 2 years were evaluated. To assess outcomes during RT weight change, treatment duration, number of appointments and formula products issued were evaluated. To assess RT adherence outcomes for those recorded as attending either more than one appointment or only one appointment. Finally, proportions achieving the RT weight loss target of ≥2 kg were evaluated. Continuous data are summarised using the mean (SD), as well as categorical data by frequencies and percentages. Those recorded as using and not using RTs were compared using *t*-tests for continuous data and Fisher's exact tests for categorical data. To assess the effect of using and not using RTs on outcomes at 2 years, mixed effects linear or logistic regression analysis was used. The regression models adjusted for baseline value of outcomes where applicable, practice list size (≤5700, >5700), study centre (Scotland or Tyneside) and a random effect for practice. An independent statistician conducted unblinded statistical analysis, using r, version 3.2.4 (R Foundation for Statistical Computing, Viennna, Austria).

Results

Study population and baseline characteristics

In total, 123/149 (83%) DiRECT intervention participants commenced the WLM phase after 26 (17%) had withdrawn prior to the WLM phase.[3] Of those starting the WLM phase, 99 (80%) regained >2 kg: 60 of those 99 (61%) were recorded as using RT and 39 (39%) were not (Fig. **1**). Weight regain >2 kg was not recorded for 24 (20%) participants, of whom 12 (50%) used RT (reasons unspecified in the dataset) (Fig. **1**).

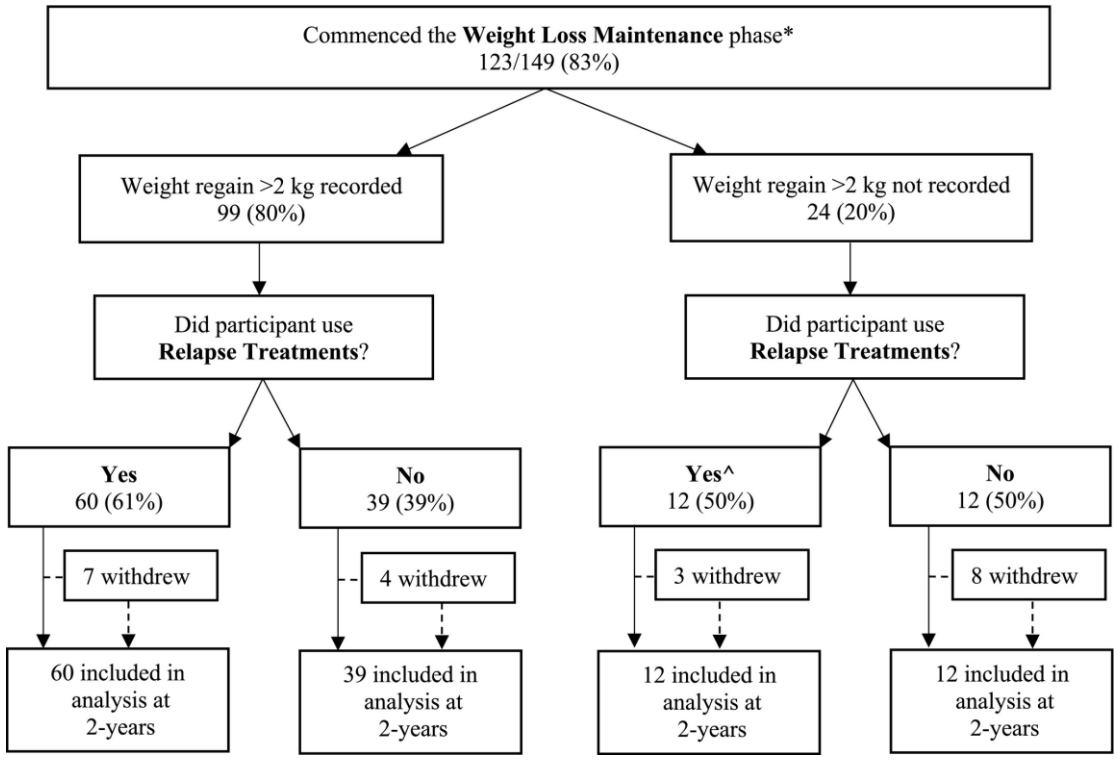

Figure 1 - Participants commencing the weight loss maintenance (WLM) phase of the Diabetes Remission Clinical Trial (DiRECT) (*n* = 123). *26 (17%) had withdrawn from the intervention prior to the WLM phase. ^The reasons why participants with recorded weight regain >2 kg used relapse treatments were not recorded in the dataset.

Of those 60/99 using RT, 39 (65%) were recorded as using one, 12 (20%) recorded using two and 9 (15%) recorded using three or more RTs (maximum 6). Mean (SD) weight regain from the start of WLM to initiation of RTs was 4.7 (4.2) kg. Baseline characteristics for the *n* = 99 who qualified for RT (weight regain >2 kg) and were recorded as using or not using RTs are presented in Table **1**. Similar baseline characteristics were observed, although RTs users had a higher BMI [35.8 (4.9) kg m^{-2} vs. 33.8 (3.9) kg m^{-2}, $p = 0.0231$] and greater social deprivation ($p = 0.0003$) than non-users. Orlistat was prescribed to only three participants during the WLM phase for up to 2 years; therefore, no further analysis was conducted.

Table 1 - Baseline characteristics for those eligible for (regaining >2 kg) and recorded as using or not using relapse treatments (RT) (*n* = 99) during the weight loss maintenance phase of the Diabetes Remission Clinical Trial (DiRECT)

Baseline Characteristics	**Participants regaining >2 kg and recorded as using or not using relapse treatments (RT)**		***p*-value***
	Mean (SD)		
	Used RT	**No RT**	
n	60	39	
Males *n* (%)	32 (53)	25 (64)	0.3071
Age (years)	53.3 (6.7)	54.7 (6.9)	0.3020

Baseline Characteristics	Participants regaining >2 kg and recorded as using or not using relapse treatments (RT)		*p*-value*
	Mean (SD)		
	Used RT	No RT	
Weight (kg)	101.4 (16.3)	97.9 (15.3)	0.2736
Body mass index (kg m^{-2})	35.8 (4.9)	33.8 (3.9)	**0.0231**
Duration type 2 diabetes (years)	3.0 (1.5)	3.1 (1.8)	0.8723
HbA_{1c} (mmol mol^{-1})	58.2 (11.6)	59.3 (10.2)	0.6087
Prescribed oral anti-diabetic drugs, *n* (%)	43 (72)	28 (72)	1.0000
Systolic blood pressure (mmHg)	135.4 (16.4)	131.5 (18.6)	0.2882
Diastolic blood pressure (mmHg)	84.4 (8.5)	84.8 (11.4)	0.8549
Prescribed anti-hypertensive drugs, *n* (%)	32 (53)	22 (56)	0.8376
Total cholesterol (mmol L^{-1})	4.46 (0.90)	4.04 (1.15)	0.0674
High-density lipoprotein cholesterol (mmol L^{-1})	1.08 (0.21)	1.09 (0.28)	0.8264
Triglycerides (mmol L^{-1})	2.17 (1.54)	1.75 (0.91)	0.0983
Quality of life			
EQ-5D Health Utility Score	0.795 (0.259)	0.859 (0.266)	0.2427
EQ-5D VAS	66.6 (16.6)	68.6 (19.6)	0.6074
Index of Multiple Deprivation, quintile *n* (%)[a]			
Q1–Most deprived	11 (19)	5 (13)	**0.0003**
Q2	16 (28)	0 (0)	
Q3	12 (21)	17 (44)	
Q4	8 (14)	11 (28)	
Q5–Least deprived	11 (19)	6 (15)	

[a] Missing data index of multiple deprivation, $n = 2$ (all in used relapse treatment group).
p-value is the difference between those eligible for and using or not using relapse treatments. Fisher's exact test were used to test for differences in categorical data and *t*-tests were employed for continuous data.

Weight change, type 2 diabetes remissions and programme withdrawals at 2 years

At 2 years, those regaining >2 kg and recorded as using RT (*n* = 60) had mean (SD) weight losses of 7.4 (6.1) kg, with 25 (42%) remissions and 7 (12%) programme withdrawals. Those regaining >2 kg but not recorded as using RT (*n* = 39) had weight losses of 8.8 (6.0) kg, with 21 (54%) remissions and 4 (10%) programme withdrawals (all not significant) (Table **2**). At 2 years, those recorded as using RT on either 1, 2 and 3 or more occasions had weight losses of 7.8 (7.1) kg, 6.8 (4.3) kg and 6.7 (3.6) kg ($p = 0.8435$), with 17 (44%), 4 (33%) and 4 (44%) remissions ($p = 0.8621$), and 6 (15%), 1 (8%) and 0 (0%) programme withdrawals ($p = 0.7125$), respectively.

Table 2 - Two-year weight losses, remissions and programme withdrawals for those eligible or not for relapse treatment (RT) and using or not using RT during the weight loss maintenance phase of the Diabetes Remission Clinical Trial (DiRECT)

	Eligible for relapse treatment (RT) (recorded weight regain >2 kg) Mean (SD)			***p*-value***	**Not eligible for relapse treatment (RT) (no recorded weight regain >2 kg) Mean (SD)**			***p*-value**
Outcomes at 2 years	**All**	**Used RT**	**No RT**		**All**	**Used RT**	**No RT**	
n	99	60	39		24	12	12	
Weight losses (kg)	8.0 (6.1)	7.4 (6.1)	8.8 (6.0)	0.2807	9.7 (7.5)	7.4 (5.3)	12.9 (9.2)	0.1641
Remissions, *n* (%)	46 (47)	25 (42)	21 (54)	0.3031	6 (25)	2 (17)	4 (33)	0.6404
Programme withdrawals, *n* (%)	11 (11)	7 (12)	4 (10)	1.0000	11 (46)	3 (25)	8 (67)	0.0995

***p*-value is for the difference between those recorded as using and not using RT using Fisher's exact test for categorical data and *t*-tests for continuous data.**

Twenty-four participants never regained >2 kg, demonstrating 2-year weight losses of 9.7 (7.5) kg, with 6 (25%) remissions and 11 (46%) programme withdrawals. However, *n* = 12 used RT (reasons not specified), demonstrating 2-year weight losses of 7.4 (5.3) kg, with 2 (17%) remissions and 2 (25%) programme withdrawals, and *n* = 12 did not use RT, demonstraing 2-year weight losses of 12.9 (9.2) kg, with 4 (33%) remissions and 8 (67%) programme withdrawals (all not significant) (Table **2**).

During relapse treatment outcomes

The 60 participants who regained >2 kg were recorded as using a total of 93 RTs during the 18-month WLM phase. The mean (SD) number of appointments attended during RT was 2.8 (1.5) and mean (SD) weight losses were 0.5 (3.8) kg. At the end of the RT, 30/93 (32%) had achieved ≥2 kg weight loss (i.e. corrected their regain).

Those using FR for a 4-week RT (with two, reducing to one, formula meal replacement per day) or TDR for a 4-week RT had weight losses of 0.4 (3.0) kg versus 0.7 (2.6) kg, respectively. The mean (SD) duration for FR RT was 7.0 (4.1) weeks compared to 5.5 (4.3) weeks for RT TDR, and 60 (57) versus 66 (40) formula products were issued during the RT, respectively. Given the amount of formula products issued for RT, each TDR RT would have lasted 2 weeks if used exclusively as a TDR. During RT, those attending more than one appointment had significantly greater weight change [−0.9 (4.1) kg vs. 0.7 (2.2) kg, $p = 0.0241$] and a larger proportion achieved ≥2 kg weight loss [29 (40%) vs. 1 (5%), $p = 0.0014$] than those attending only 1 appointment, respectively (see Supporting information, **Figure S1**a and b).

Association between using and not using relapse treatments on outcomes at 2 years

Using regression modelling controlling for practice list size, study centre and random effect for practice, we assessed the association between those using and not using RTs on outcomes at 2 years (see Supporting information, Table **S1**). Those recorded as using RTs ($n = 60$), had a lower systolic blood pressure at 2 years than those not using RTs ($n = 39$) [adjusted mean difference in mmHg, −6.00, 95% confidence interval (CI) = −11.91 to −0.08; $p = 0.0469$], even though no significant between group difference in the prescriptions of anti-hypertensive medications was observed (1.40, 95% CI = 0.47–4.22; $p = 0.5474$). Furthermore, those recorded as using RTs had a lower quality of life at 2 years (measured with the EQ-5D 100-point Visual Analogue Scale) than those not using RT (adjusted mean difference in points, −6.26, 95% CI = −12.42 to −0.10; $p = 0.0465$).[1] For all other outcomes, there were no significant differences between those recorded as using and not using RT.

Discussion

Most participants in DiRECT (80%) experienced some weight regain within 2 years, although less than has been reported with other weight management programmes.[20] Similar weight losses, remissions and programme withdrawals were observed for those qualifying for (regaining >2 kg) and using and not using RT [7.4 (6.1) kg and 8.8 (6.0) kg, respectively], However, in those never regaining >2 kg (24/123), a greater weight loss of 12.9 (9.2) kg was observed in the 12/24 (50%) in this category not using RTs.

Although the knowledge that RT would be offered if needed may have had value for optimising uptake, adherence and the overall results of the Counterweight-Plus programme in DiRECT, in practice, RTs were often not used as soon as >2 kg regain was recorded. This represents a minor deviation from protocol, for reasons unspecified but probably including both participant preferences and practitioner judgements. The weight losses during RTs (mean 0.5 kg) were well below what would occur given full adherence to a 4-week period of TDR (approximately 830 kcal day^{-1}) or FR (approximately 1000–1400 kcal day^{-1}). Around one-third (32%) of RT attempts achieved >2 kg weight loss (i.e. corrected 2-kg regain, which triggered RT use). However, the 2-year weight losses for those receiving RT in DIRECT were similar [7.4 (6.1) kg] to those who were eligible for but never received, RTs [8.8 (6.0) kg]. Remission rates and programme withdrawals were also similar, which may introduce doubt as to the value of this approach to RT. We expected participants using

multiple RTs would perform less well, and be more likely to disengage from the weight management programme. However, those who required and used multiple RTs did not have inferior outcomes at 2 years. The evidence did not indicate greater success with a 4-week TDR RT than a 4-week FR RT, although greater RT appointment attendance resulted in improved weight losses during RT. Anecdotal reports suggested that participants valued the potential availability of RT, as part of the protocol. This suggests that there is value in offering RT as part of a structured weight management package, although further qualitative studies are needed to confirm their value for practitioners and participants.

To our knowledge, the application of LED for RT has not previously been studied in people with T2D in a primary care setting, or included in a structured protocol as in DiRECT. RT allows both practitioners and participants to acknowledge that weight regain occurs and agree collaboratively to address the regain. In DiRECT, RTs with a short return to TDR or FR were the only options offered to treat regain.[1] Lacking other options, treatment fatigue (because participants had already used LED for weight loss) may have contributed to the disappointing weight losses observed during RTs. Additional strategies to treat regain are needed, potentially environmental, behavioural and pharmaceutical.[2] Although orlistat was offered after RT in the protocol, less than 5% of DiRECT participants accepted it. More recent and more potent anti-obesity medications such as glucagon-like peptide-1 agonists may hold promise if they can be approved for WLM.[21] At baseline, RT users were from more socially deprived areas and, by 2 years, had a lower quality of life than those not using RT. However, these findings did not result in differences in either weight loss or remissions at 2 years, possibly as a result of the exploratory nature of our study. Previously, DiRECT reported remission was less likely at 2 years for those from socially deprived areas, possibly as a result of participants lower quality of life and subsequent impact on behaviours.[22] Future studies should examine the relationship between social deprivation, quality of life, RT use and impact on weight management programme performance.

WLM is challenging.[9] Most participants welcome ongoing support from healthcare professionals, yet evidence is lacking for efficacy.[22, 23] Little research effort has been made with respect to sustaining weight loss long-term, and full recovery from relapse has rarely been observed in practice, leading to the notion that obesity is inevitably progressive.[9, 24] For the routine implementation of Counterweight-Plus, the RT protocol should be revised to identify those who would not benefit from continuing RTs and aim to address external barriers (e.g. life events) before undertaking RT.[11] Furthermore, weight regain occurred during FR for some participants; therefore, having the option to use RTs during FR, the critical time-point when new behaviours are being established, may improve outcomes.

There is no doubt that TDR is difficult socially, although well-accepted for primary weight loss.[25-27] Routine delivery of the same weight management programme used in DiRECT found similar weight losses but only 14% of participants used RTs up to 1 year.[18] A recent TDR weight management study included the option of using a RT TDR for 4 weeks if regain was >1 kg between 13 and 24 weeks. However, not one participant used this option: instead, 38% had contact with the commercial 'counsellors' who delivered the TDR weight management programme. It was assumed these participants continued to purchase formula products for use from the end of the weight loss phase to 12 months.[28]

The RT method using in DiRECT is resource intensive; requiring additional practitioner time, formula diet sachets and resources, leading to clinically

insignificant (approximately 0.5 kg) weight losses for all RT users, but successfully correcting weight regain for one-third of participants, reflecting the value of this approach for a subset of participants, although suggesting the need for a wider portfolio of options. The complete 2-year Counterweight-Plus weight management programme (including relapse treatments) has been demonstrated to be both cost-effective and cost saving, justifying the inclusion of RT as part of the structured WLM offering.[29]

Limitations

As previously stated, this was a post-hoc analysis and so chance findings are possible, and the results may not indicate causality.[30] The RTs were optional, with their use depending on individual circumstances and agreements between practitioners and participants, and data were not collected regarding specific triggering indications or whether practitioners offered treatments as per the study protocol, nor about why participants used or did not use RTs. Participants already had the option to use daily meal replacements as a routine WLM strategy within the DiRECT protocol, and so a return to more intensive sachet usage may have lacked novelty and impaired adherence to RTs. Without a control group and random allocation of RTs to participants, we cannot make formal conclusions around the effectiveness of RTs; however, the data can inform further research trials and assist with programme improvements.

Conclusions

Weight regain is the biggest challenge facing people who seek sustained weight loss and remission of T2D. In a primary care setting, few treatments exist to treat weight regain. Most people with T2D (80%) experienced regain >2 kg during 2 years after substantial weight loss with LED. Only one-third of RTs corrected regain, resulting in weight losses, remissions and programme withdrawals at 2 years similar to those not using RTs, although both groups had weight losses below those not recorded as regaining >2 kg during the WLM phase of DiRECT. Prospective studies are required to determine the extent of benefit of this planned approach, as well as other options, to treat weight regain and sustain T2D remissions.

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Conflict of Interest

MEJL reports research grants and personal fees for lecturing and consultancy from Novo Nordisk and consultancy fees from Counterweight Ltd, Novartis and Eli Lilly. RT reports educational lecture fees from Eli Lilly and Novartis and advisory board fees from Wilmington Healthcare. NB was previously employed by Counterweight Ltd and reports personal fees for freelance work and shareholdings from Counterweight Ltd and funding of PhD fees and conference attendance from Cambridge Weight Plan. AB reports speaker honoraria from Novo Nordisk, Napp

Pharmaceuticals and Eli Lilly. LM was previously employed by Counterweight Ltd and reports research funding from Cambridge Weight Plan and consultancy fees from Counterweight Ltd. GT reports funding of PhD fees and conference expenses from Cambridge Weight Plan. WSL reports conference expenses from Cambridge Weight Plan. NS reports research grants and speaker's honoraria from Boehringer Ingelheim and speaker's honoraria from Amgen, AstraZeneca, Eli Lilly, Napp Pharmaceuticals, Novo Nordisk and Sanofi. All other authors declare that they have no conflicts of interest.

Author Contribution

ML and RT conceived the DiRECT study and are the principal investigators. A contribution statement for the original DiRECT study has been published previously.[2, 3] For the present study, NB and ML conceived and designed this post-hoc evaluation. CMM and AM conducted the statistical analysis. NB and ML drafted the manuscript with input from WL and LM. All other authors (AB, GT, NS) critically reviewed and revised the manuscript and have read and approved the final version submitted for publication. All authors agree to be accountable for all aspects of the work in respect of accuracy and integrity. Overall, ML and RT are the guarantors of this work, had full access to all study data, and take responsibility for the integrity of the data and the accuracy of the data analyses.

Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with CONSORT guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned ISRCTN03267836 **www.controlled-trials.com/ISRCTN03267836** have been explained.

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