

Update on diabetes remission and diabetes remission maintenance

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Disclosures

Medical Director,
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(European industry group)





<https://tdmr-europe.com/>

■ Videos:

■ Index page:

– <https://tdmr-europe.com/2020/08/04/tdmr-europe-reducing-future-risk-obesity-co-morbidities-and-nutritional-status-index-page/>

■ Mike Lean – DiRECT trial:

– <https://tdmr-europe.com/2020/08/04/reducing-future-risk-obesity-co-morbidities-and-nutritional-status-mike-lean/>

■ Henning Bliddal – Osteoarthritis trial:

– <https://tdmr-europe.com/2020/08/04/tdmr-europe-webinar-tdr-and-vitamin-d-status-in-elderly-obese-people-with-knee-osteoarthritis-henning-bliddal/>

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<https://tdmr-europe.com/>

- Summaries:
- PREVIEW – diabetes prevention with initial TDR
 - <https://tdmr-europe.com/2020/11/25/prevention-of-diabetes-through-lifestyle-intervention-in-europe-and-australasia-preview/>
- DIADEM study – type 2DM remission in Middle East
 - <https://tdmr-europe.com/2020/05/22/intensive-life-style-intervention-including-initial-weight-loss-with-tdr-delivered-60-diabetes-remission-in-people-with-early-type-2-diabetes-mellitus-from-the-middle-east-and-north-africa-studied-i/>
- Insulin treated diabetes:
 - <https://tdmr-europe.com/2020/02/03/total-diet-replacement-proven-to-be-effective-in-insulin-treated-type-2-diabetes/>
- Weight loss with TDR in osteoarthritis
 - <https://tdmr-europe.com/2019/09/13/the-revolution-in-osteoarthritis-care-for-the-2020s/>

Outline

- Formula diets –
 - TDR Total Diet Replacement – LED & VLED
 - MRP Meal replacement products
- Copenhagen: TDR in obese people with osteoarthritis
- Diabetes remission – DiRECT trial
- Diabetes prevention – PREVIEW trial
- Primary care/community delivery - DROPLET
- Summary
- Next Steps



Definitions

■ **TDR Total Diet Replacement**

- Formula diet providing all day's food intake

■ **LED Low energy liquid diet**

- 800kcal/d +
- 4 portions of formula food products based on skimmed milk as milk shakes or soups (or porridge or bars)
- providing 1/3 of daily needs of micronutrients per portion

■ **VLED Very Low Energy Diet**

- < 800kcal/d (e.g. 600kcal/d – 3 portions)

■ **Meal Replacement Product MRP**

- Formula product 200-250kcal/portion usually used for one or two meals daily with conventional meals

How do they work?

- **Larger energy deficit**
 - 1000 – 2000kcal/d
 - (compare to 500-600kcal/d of usual reducing diet)
- **Greater rate of weight loss** – typically 1.3kg/week in women, 1.5kg/week in men
- **High compliance** compared to conventional reducing diet
- **Better 6/12 maintenance** attributed to greater rate of weight loss (highly motivating) (DIOGENES)
- **Facilitate portion control** (American Dietetics Assoc)
- Ketosis – **appetite suppression via reduction of Ghrelin effect?**

Nutrient composition

Conform to current EU Meal Replacement specifications

- **Protein** 25 to 50% dietary energy ... 40%
~**60 – 80g** (600-800kcal) [*for 80-100kg ...0.75-1.0-0.8g/kg*]
- **Carbohydrate 60g-80g** in 6-800kcal (40% dietary energy)
- Fat ...not exceeding 30% dietary energy
- Defined lower limit for Essential Fatty Acids ®
- Dietary fibre 10g – 30g
- **Micronutrients** not less 30% RI **per portion ... 33%**
- **Nutritionally complete (compare with the deficiencies associated with low carbohydrate diets)** [\[Charuangsuk etal 2019\]](#)
- **Malnutrition of obesity can be corrected** [\[Christensen etal 2013\]](#)



Sequence of recent clinical
trials started in
Copenhagen Denmark
in 2007

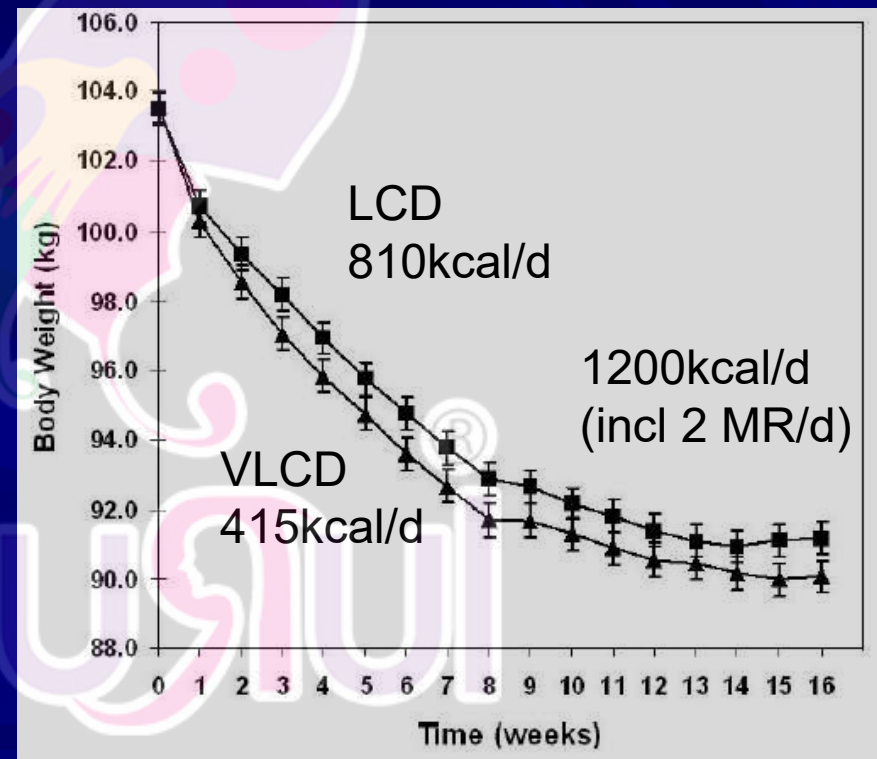
Copenhagen weight loss in elderly obese people with knee osteoarthritis trial



Key message:

- **>12% of initial body weight in both groups in 16/52**
- **60% had a significant pain reduction in both groups**

Drop Outs: 10/96 and 7/96



Riecke BF, et al Osteoarthritis and Cartilage 2010; 10/1016?j.joca.2010.02.012

Christensen P et al Clinical Obesity 2011; 1, 31-40.

Can Total Diet Replacement...

reverse early diabetes with initial weight loss of **5-15%** with maintenance?

prevent diabetes with sufficient weight loss **(10%)** followed by weight maintenance?

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Diabetes Remission Clinical Trial in early type 2 diabetes



Funded by Diabetes UK



Newcastle,
northern England



Glasgow,
southern Scotland

Formula diet products for the weight loss phase and 'rescue packages' supplied by Cambridge Weight Plan

Lean MEJ et al Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised Trial [The Lancet 2018 391, p541–551](#)



- 298 subjects, ~30 practices in Scotland and North-East England
primary care setting
- Usual care or 810kcal/d TDR followed by maintenance delivered by health care professionals using a dietitian-led programme*

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* [Counterweight-Plus dietitian-led programme](#)

Lean MEJ et al Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised Trial [The Lancet 2018 391, p541–551](#)



- Women & Men aged 20 to 65y, Type 2 diabetes for 0 to 6 years duration (non insulin-treated)
- BMI $>27\text{kg/m}^2$ to $<45\text{kg/m}^2$
- participants were followed up at 1 and 2 years and will be followed for 5 years (ends 2022)

One year primary end-points:



Weight loss of > 15kg at one year

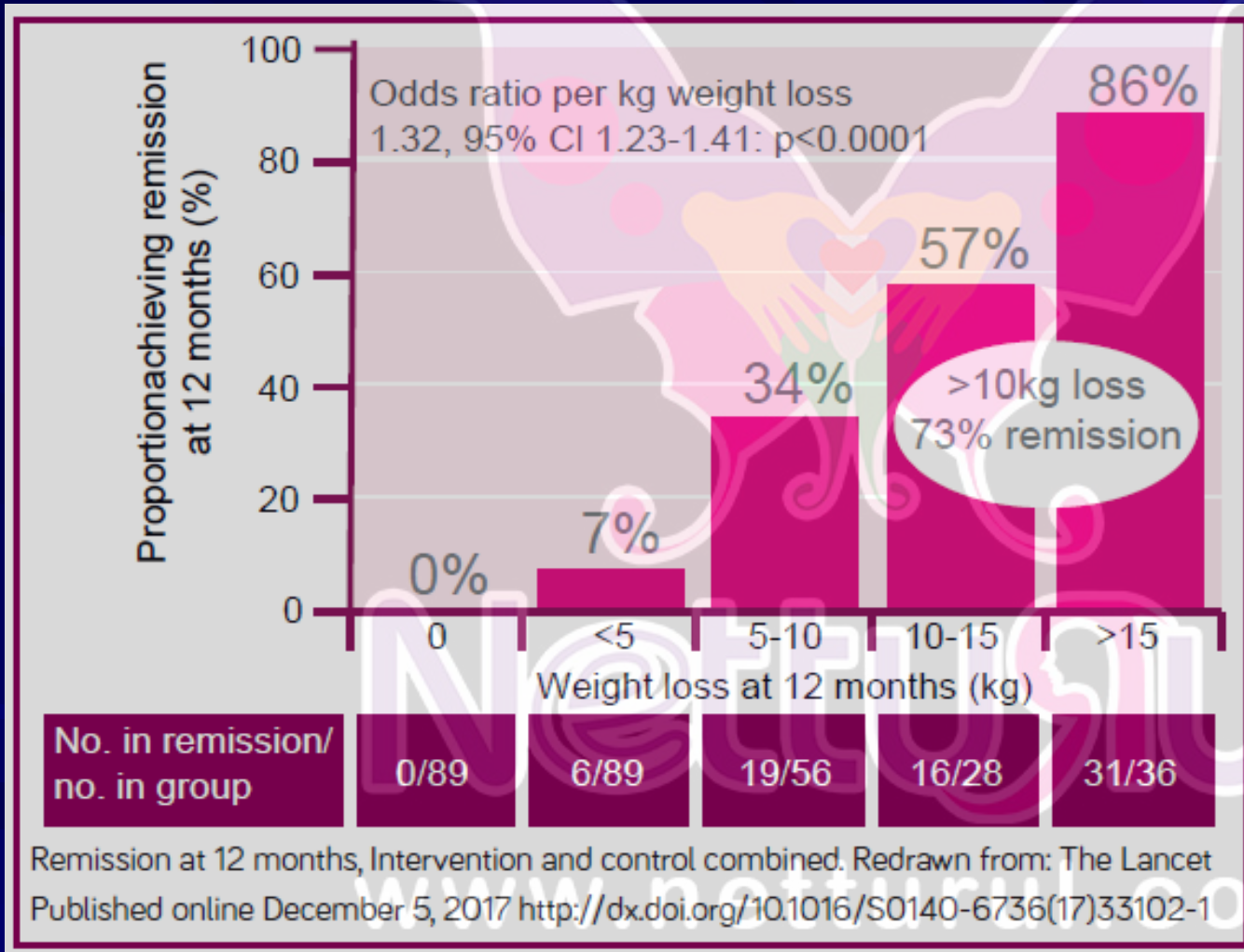
- TDR 36/149 participants (24%)
 - Usual NHS care 0/149
- $p < 0.0001$

Remission of diabetes (HbA1C <48 mmol/mol)

- TDR 68/149 (46%)
 - Usual NHS care 6/149
- $p < 0.0001$

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TDR and control combined



KEY MESSAGE:
>10kg weight loss, maintained at one year gives diabetes remission in 3 out of 4 people

KEY MESSAGE:

Huge reduction in medication use AND Improved Quality of Life

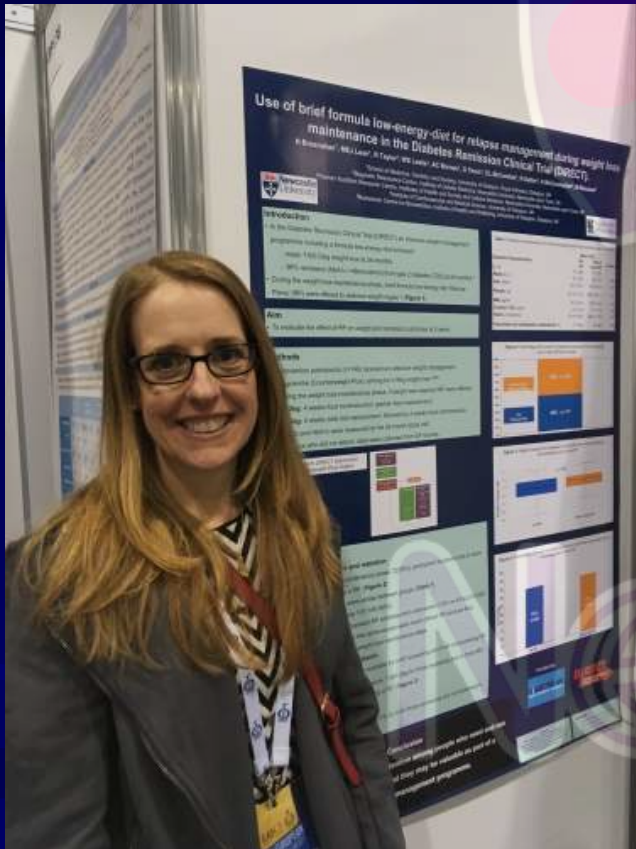


At one year	Total Diet replacement	NHS Best Practice
On anti-diabetes medications	Reduction of 78%	Reduction of 18%
On medications for high blood pressure	Reduction of 68%	Reduction of 39%
Quality of Life (EQ5)	Increase of 11%	Decrease of 4%

Use of brief formula low-energy diet for relapse management during weight loss maintenance in DiRECT

Brosnahan N, Lean MEJ, Taylor R, et al poster at ECO2019

European Congress on Obesity Glasgow Monday 29th April 2019



Rescue plans

- If weight regain >2kg ... 4 weeks food reintroduction phase with MRP
- If weight regain >4kg ... 4 weeks TDR then 4 weeks food reintroduction

n =143 in the intervention group

- **50% needed one or more rescue plan**
- **Of 53 participants who achieved remission at 24 months half had used one or more rescue plan.**

KEY MESSAGE: include resources for 50% of participants to need 4 weeks+ TDR as rescue package in first 2 years

Lean MEJ et al 2019 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 and Endocrinology Published Online March 6, 2019
[http://dx.doi.org/10.1016/S2213-8587\(19\)30068-3](http://dx.doi.org/10.1016/S2213-8587(19)30068-3)

Weight loss maintained at year 1 or year 2

	<5kg	5-<10kg	10-<15kg	>15kg
Year 1	4	34	57	86
Year 2	5	29	60	70

**Proportion
in
Remission
as %**

**63% in remission
>10kg weight loss at 2 years**

Remission of type 2 diabetes in relation to weight loss achieved
(both randomised groups combined).

**KEY MESSAGE: >10kg weight loss, maintained at two years
gives diabetes remission in 2 out of 3 people**

Lean MEJ et al 2019 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 and Endocrinology Published Online March 6, 2019
[http://dx.doi.org/10.1016/S2213-8587\(19\)30068-3](http://dx.doi.org/10.1016/S2213-8587(19)30068-3)
[https://www.thelancet.com/journals/landia/article/PIIS2213-8587\(19\)30068-3/fulltext](https://www.thelancet.com/journals/landia/article/PIIS2213-8587(19)30068-3/fulltext)

‘The DiRECT programme sustained remissions at 24 months for more than a third of people with type 2 diabetes. Sustained remission was linked to the extent of sustained weight loss.’

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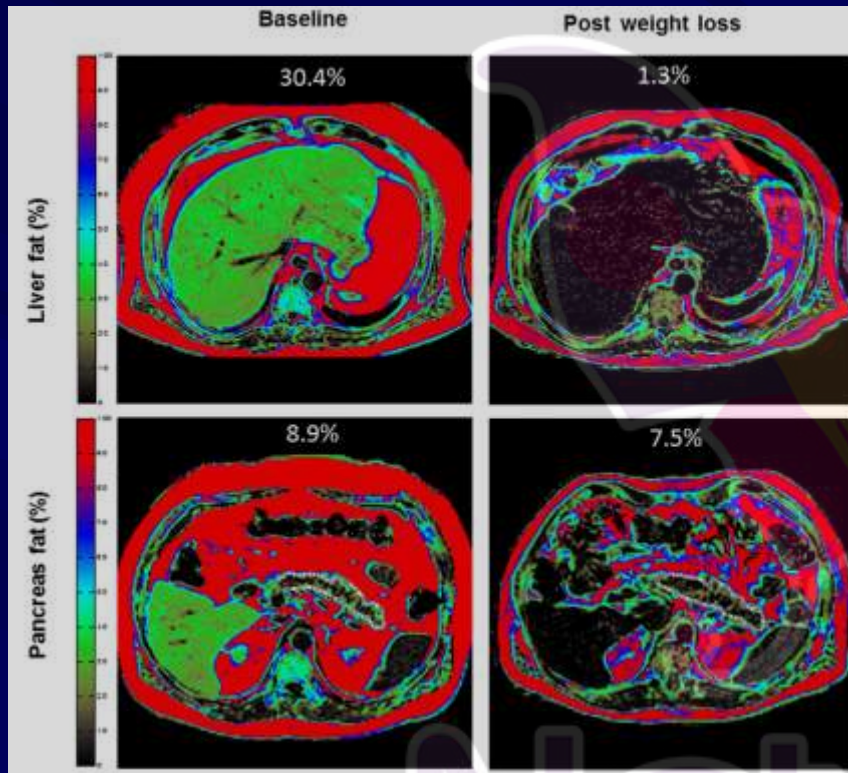
Taylor R, Al-Mrabeh A, Zhyzhneuskaya S et al 2018 Remission of Human Type 2 Diabetes Requires Decrease in Liver and Pancreas Fat Content but Is Dependent upon Capacity for Beta Cell Recovery' Cell Metabolism
<https://doi.org/10.1016/j.cmet.2018.07.003>

A subset of DiRECT participants from the Newcastle area (64 TDR diet; 26 usual care) were scanned for liver and pancreatic fat at baseline, after weight loss (around 5 months) and at 12 months;

Those in diabetes remission at 1 year were defined as 'responders':

- **Responders** lost 16.2kg (16%) but regained 3.3kg during maintenance (**lost more and regained less**);
- **Non-responders** lost 13.4kg but regained 4.9kg during maintenance (**lost less and regained more**);

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- **Maintenance of remission** was associated with
- **more effective weight maintenance,**
 - **more effective maintenance of liver fat reduction,**
 - *more pronounced rise of blood ketones and maintenance of blood ketones at one year.*
[linked to degree of energy restriction]

KEY MESSAGE: ‘Responders’ lost more weight and regained less weight possibly reflecting tighter energy intake control during maintenance

2-year remission of type 2 diabetes and pancreas morphology: a post-hoc analysis of the DiRECT open-label, cluster-randomised trial
Al-Mrabeh A et al, Lancet Diabetes Endocrinol 2020

Published Online
October 5, 2020

[https://doi.org/10.1016/S2213-8587\(20\)30303-X](https://doi.org/10.1016/S2213-8587(20)30303-X)

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Go to Figure 3 in
Online paper

[https://www.thelancet.com/journals/landia/article/PIIS2213-8587\(20\)30303-X/fulltext](https://www.thelancet.com/journals/landia/article/PIIS2213-8587(20)30303-X/fulltext)

'In conclusion, our results suggest that the small, irregular pancreas typical of type 2 diabetes is secondary to the disease state itself and returns towards normal during 2 years of dietary weight loss-induced remission.'

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Can Total Diet Replacement...

reverse early diabetes with initial weight loss of 5-15% with maintenance?

- **>10kg weight loss delivered diabetes remission in 3 out of 4 people at one year;**
- **and in ~2 out of 3 people at two years;**
- **‘Responders’ lost more weight and regained less weight possibly reflecting tighter energy intake control;**

Can Total Diet Replacement...

reverse early diabetes with initial weight loss of 5-15% with maintenance?

- **'Rescue packages' were needed by 50% of responders;**
- **Pancreatic morphology reversible to normal.**

Can weight loss, and diabetes remission be maintained for 5 years? the study continues...

NHS Scotland: in use; NHS England: roll-out under way

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Taheri S et al 2020 Effect of intensive lifestyle intervention
On bodyweight and glycaemia in early type 2 diabetes (DIADEM-1):
an open label, parallel-group, randomised controlled trial
Lancet Diabetes Endocrinology 2020 8 (6): 477-489
DOI: [https://doi.org/10.1016/S2213-8587\(20\)30117-0](https://doi.org/10.1016/S2213-8587(20)30117-0)

- 107 men 40 women
18-50years-old from
Middle East & North
Africa

- T2diabetes <3years

- RCT in primary care

- 70 800kcal/d TDR for 12
weeks then food
reintroduction and
maintenance

- 77 usual care

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<https://onlinelibrary.wiley.com/doi/epdf/10.1002/oby.22407>

- 12kg versus 4kg weight
loss at 12 months

Taheri S et al 2020 Effect of intensive lifestyle intervention
On bodyweight and glycaemia in early type 2 diabetes (DIADEM-1):
an open label, parallel-group, randomised controlled trial
Lancet Diabetes Endocrinology 2020 8 (6): 477-489
DOI: [https://doi.org/10.1016/S2213-8587\(20\)30117-0](https://doi.org/10.1016/S2213-8587(20)30117-0)

medications	Intervention group	Usual Care control
anti-diabetes	90% reduced	11% increase
anti-hypertensive	40% reduced	37% increase

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<https://onlinelibrary.wiley.com/doi/epdf/10.1002/oby.22407>

Remission at 12 months:

61% intervention group

12% control group

Key message:

**TDR is effective in a
Middle-East population**



Can Total Diet Replacement...

prevent diabetes with sufficient weight loss **(10%)**
followed by weight maintenance?

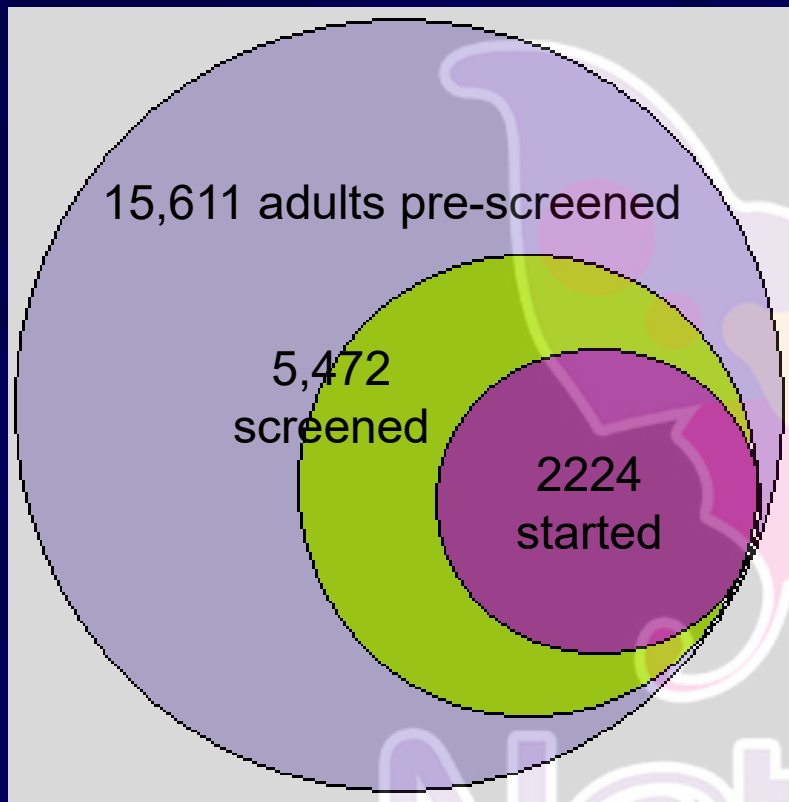
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PREVIEW

PREvention of diabetes through lifestyle Intervention and population studies in Europe and around the World



2224 people with pre-diabetes (ADA criteria) and overweight started a 3 year diabetes-prevention programme with a **Total Diet Replacement 800kcal/d for 8 weeks**





PREVIEW

PREvention of diabetes through lifestyle Intervention and population studies in Europe and around the World



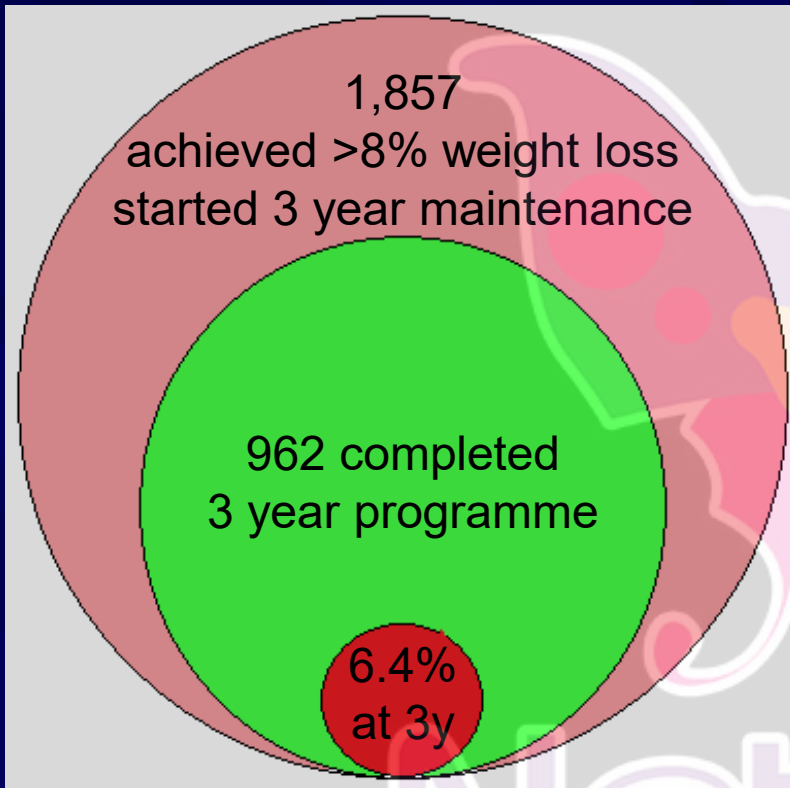
HIGH COMPLIANCE:

- 91% completed the diet;
- **Weight loss average 10.7kg in 8 weeks;**
- 83.5% achieved the target of $\geq 8\%$ weight loss at 8 weeks and started 3 year maintenance;

• **62.6% not pre-diabetic (WHO criteria) if weight loss $\geq 8\%$.**

PREVIEW

PREvention of diabetes through lifestyle Intervention and population studies in Europe and around the World



Three year weight maintenance programme:

A) lowGI+high protein

B) higherGI+lower protein

AND high versus lower exercise:

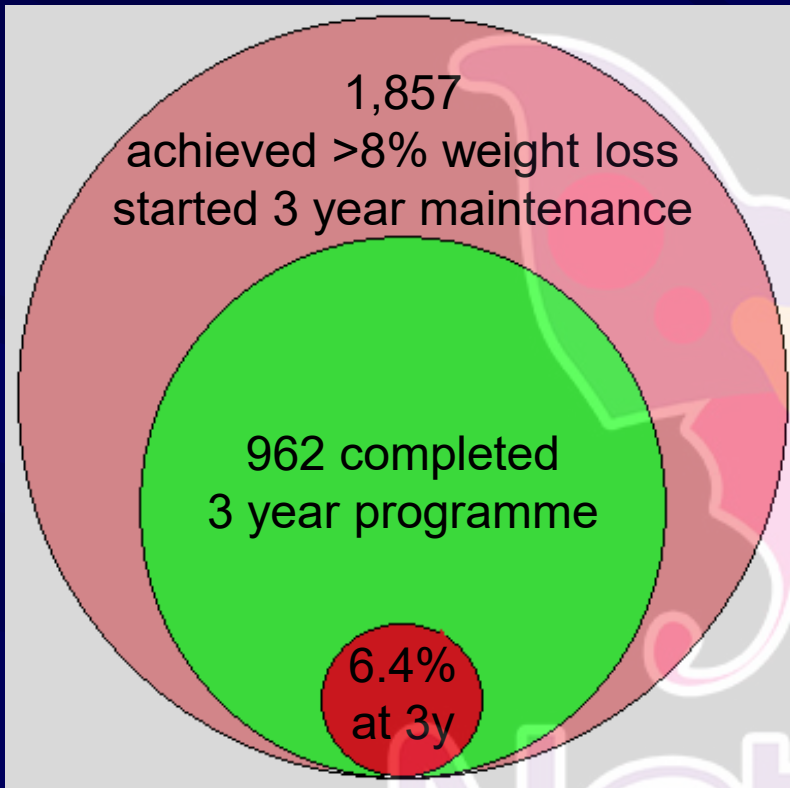
- **52% completed 3 year weight-maintenance**
- **3 year Weight loss maintenance 4.6-4.9kg in 4 groups (no significant differences)**

PREVIEW - Results from a 3-year randomised 2 x 2 factorial multinational trial investigating the role of protein, glycemic index and physical activity for prevention of type-2 diabetes. Raben A et al 2020 [doi:10.1111/dom.14219](https://doi.org/10.1111/dom.14219) Oct 2020



PREVIEW

PREvention of diabetes through lifestyle Intervention and population studies in Europe and around the World



- Only 62/962 (6.4%) developed diabetes by 3 years
- **At 3 years fewer participants developed diabetes in PREVIEW** than in Finnish (9%) or US (14%) diabetes prevention programmes (in which weight losses at 3 years were 3-4kg)

Can Total Diet Replacement...

prevent diabetes with sufficient weight loss (10%)
followed by weight maintenance?

**10% average weight loss delivered in 4 out of
5 people in 8 weeks**

**4.6 - 4.9kg average weight loss maintained at
3 years**

**6.4% developed diabetes at 3 years
(lower than expected)**



Can Total Diet Replacement...

be delivered effectively in a primary care setting with GP referral for delivery in the community?

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DROPLET ‘**D**octor **R**eferral of **O**verweight **P**eople for **L**ow **E**nergy **T**reatment’



Nuffield Department of
Primary Care
Health Sciences,
University of Oxford

Setting: Primary Care/Community

NHS primary care doctors randomly allocated obese patients to usual care (UC) or to a Cambridge Weight Plan Consultant for an 810kcal/d weight loss programme (TDR), followed by maintenance for up to one year.

Participants were recruited from around Oxford and Bicester between January and July 2016.

Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic randomised controlled trial. Astbury NM, Aveyard P, Nickless A, Hood K, Corfield K, Lowe R, Jebb SA. [BMJ 2018; 362:k3760](https://doi.org/10.1136/bmj.k3760) <http://dx.doi.org/10.1136/bmj.k3760> (September 2018)

Estimated weight change over 12 months in the intention to treat population

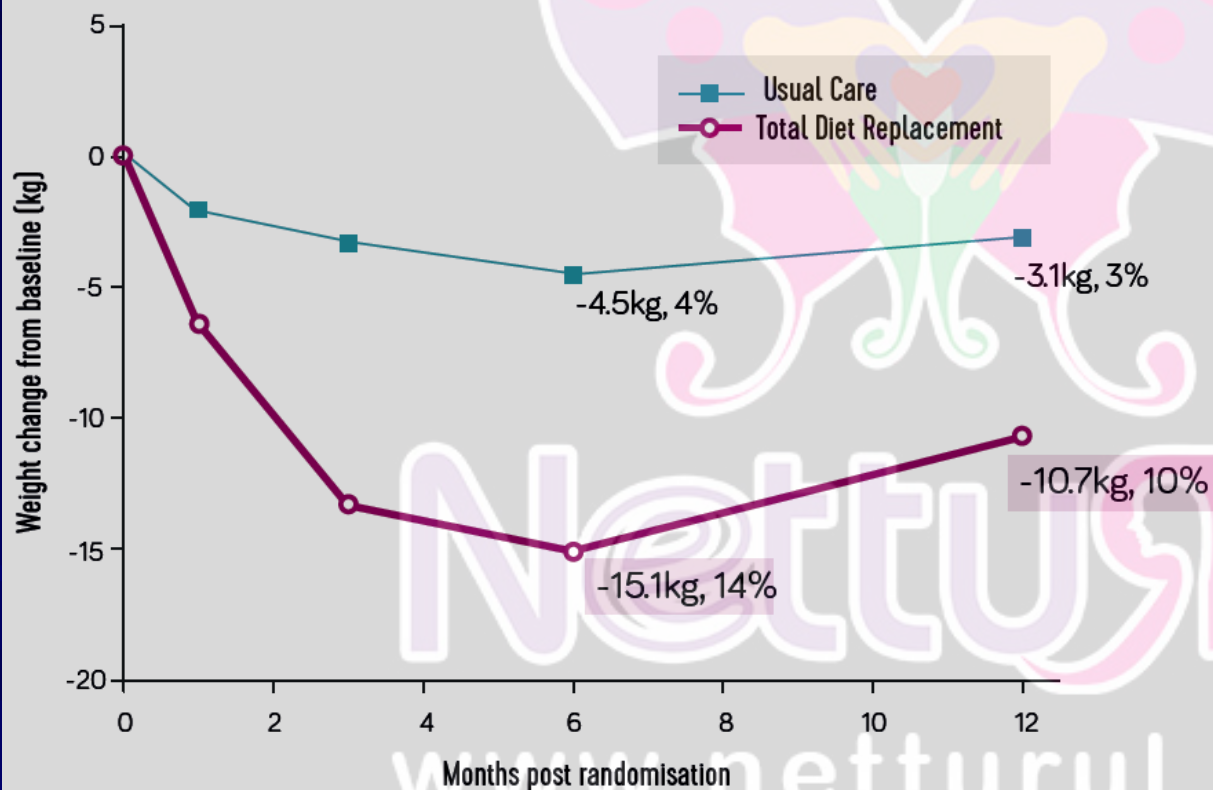


Figure redrawn from Astbury N et al *BMJ* 2018; 362: k3760 doi: 10.1136/bmj.k3760

Usual Care
Practice nurse
Using BHF weight management booklet

Total Diet Replacement
Cambridge Consultant
TDR plus behavioural support:
Goal setting
Feedback
Encouragement
Reassurance
Problem solving

Contact time not matched
TDR more than Usual Care

TOTAL DIET REPLACEMENT PROGRAMMES –
RESOURCES FOR HEALTH PROFESSIONALS available on the website of
Nuffield Department of Primary Care Health Sciences
Please see: <https://www.phc.ox.ac.uk/research/diet-plans/tdrresources-for-health-professionals>

Medication adjustment guide

This guidance aims to help you make these medication adjustments, but please use your clinical judgement.

TYPE 2 DIABETES

Patient currently takes:	Recommendation
Metformin	HALF daily dose
Sulphonylurea	STOP
Glitazone	STOP
Glinide	STOP
DPP IV inhibitor	STOP
Acarbose	STOP

At the end of the weight loss phase, re-assess patients requirements for oral diabetic therapies using HbA1c measurements or a finger prick blood glucose measurement.

KEY MESSAGE: Anticipating doctors' anxieties about medication dosage changes Oxford group provide on-line guidance.

Is Doctor referral to a low-energy total diet replacement program cost-effective for the routine treatment of obesity?

Kent S, Aveyard P, Astbury N, Borislava M, Jebb SA. Obesity 2019 published online 25 02 2019 <https://doi.org/10.1002/oby.22407>

‘...with plausible long term trajectories, **TDR is projected to be cost-effective in adults with obesity** and could be considered as an option to treat obesity in routine health care settings.’

‘It is most cost-effective in middle-aged and older adults and those at higher levels of BMI, who face higher immediate risks of obesity-related diseases and premature mortality.’

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<https://onlinelibrary.wiley.com/doi/epdf/10.1002/oby.22407>

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Incremental cost-effectiveness ratios in subgroups. Error bars show 95% CIs

Astbury N et al Three year outcomes of DROPLET
published abstract withdrawn from ICOECO conference

September 2020

<https://onlinelibrary.wiley.com/doi/epdf/10.1111/obr.13115>

p69-70

‘Primary care referral to a TDR programme in the community for the treatment of obesity leads to greater weight loss than usual care. which is sustained for at least 3 years. Even without additional support after the initial weight loss intervention, two thirds of the weight loss achieved at one year was still apparent two years later.’

Full paper under review November 2020

Can Total Diet Replacement...

be delivered effectively in a primary care setting with GP referral for delivery in the community?

10% average weight loss at one year – larger than currently available weight loss programmes offered in primary care

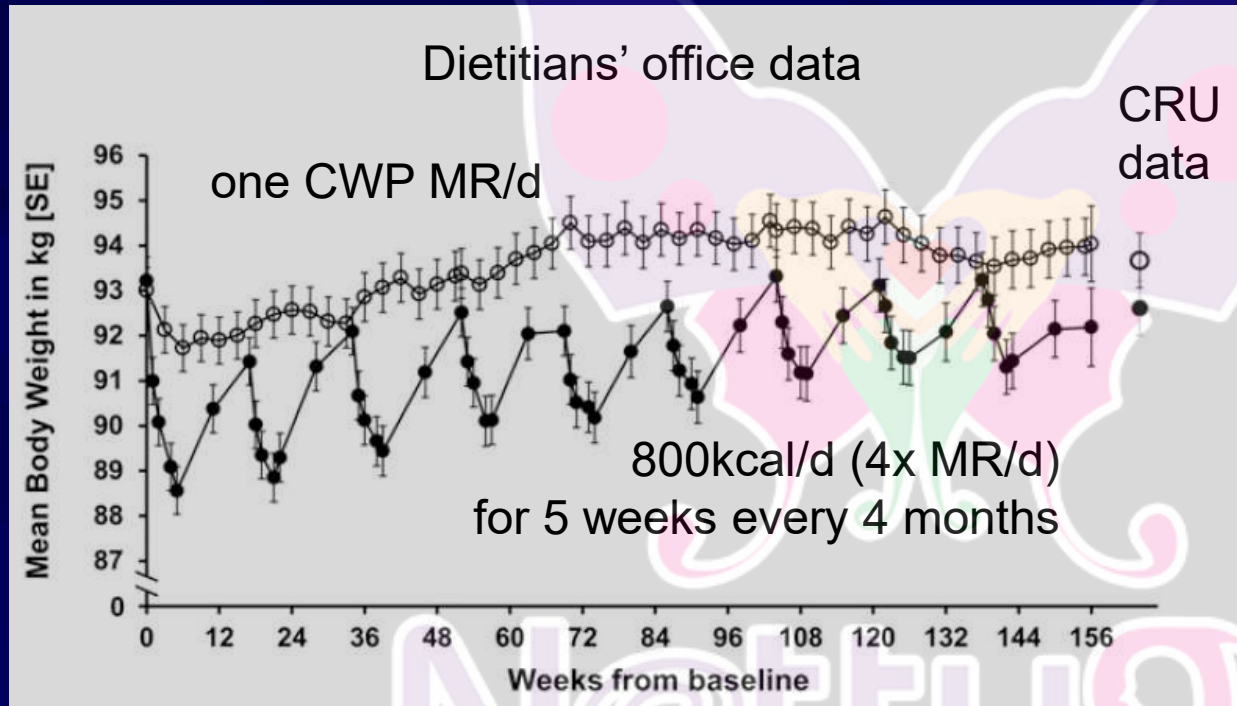
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Weight Loss maintenance

- DiRECT (diabetes remission)
 - Support & guidance from HCP on diet & lifestyle PLUS 'rescue packages'
- PREVIEW (diabetes prevention)
 - compared lowGI+high protein versus higherGI+normal protein and higher versus lesser physical activity – no difference at 3y
- Copenhagen OA trial 3 year maintenance
 - Compared 1 MRP/d versus intermittent TDR
 - 2/3 maintained ~10% weight loss for 3 years

Long-term weight-loss maintenance in obese patients with knee osteoarthritis: a randomized trial [Christensen p et al 2017](#)
[Am J Clin Nutr doi: https://doi.org/10.3945/ajcn.117.158543](#)

**3 year weight maintenance
~10%
in 106/153**



CRU data at 3 years
Weight increase:

Intermittent: 0.71kg
One MR daily: 1.78kg
(mean difference -1.07 kg; 95% CI: -2.75 to 0.62; p=0.21)

TKA surgery rates
were not different:

Intermittent: 8/76

One MR daily: 12/77

Dietitian's office data = data on available cases
CRU = Clinical Research Unit (intention to treat data)

153 subjects randomised to: one CWP MR/d or
800kcal/d (4x MR/d) for 5 weeks every 4 months
Total MR consumption in the two groups was equal

Summary

- Rising prevalence of T2 diabetes and pre-diabetes;
- Total Diet Replacement offers a potential additional intervention, especially to bridge the gap between conventional diet and bariatric surgery;
- **Fast weight loss (1.3 to 1.5kg/week) which is motivating;**
- TDR can be delivered in specialist, primary care and community settings;
- **Compliance is high** (91% in PREVIEW);
- **Safety profile is good;**
- **Reduces medication costs** (DiRECT);
- **Is cost-effective** (DROPLET) and (DiRECT);

Next Steps

- Use of TDR has to be incorporated into Clinical Guidelines;
- Address the need for education of health care practitioners.

Next steps: Maintenance diets

- Physiological factors: lose less lean mass during weight loss to minimise RMR reduction;
- Identify poor maintainers: low baseline GLP-1; provide extra help;
- Behavioural factors: impulsivity, resilience, coping strategies, need for support;
- Dietary variables: energy density, satiation effects – signalling of satiety hormones.

RESERVES

- Service Evaluation in Scotland (2 slides)
- PREVIEW adverse events (1 slide)



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McCombie L et al Filling the intervention gap: **service evaluation** of an intensive nonsurgical weight management programme for severe and complex obesity.

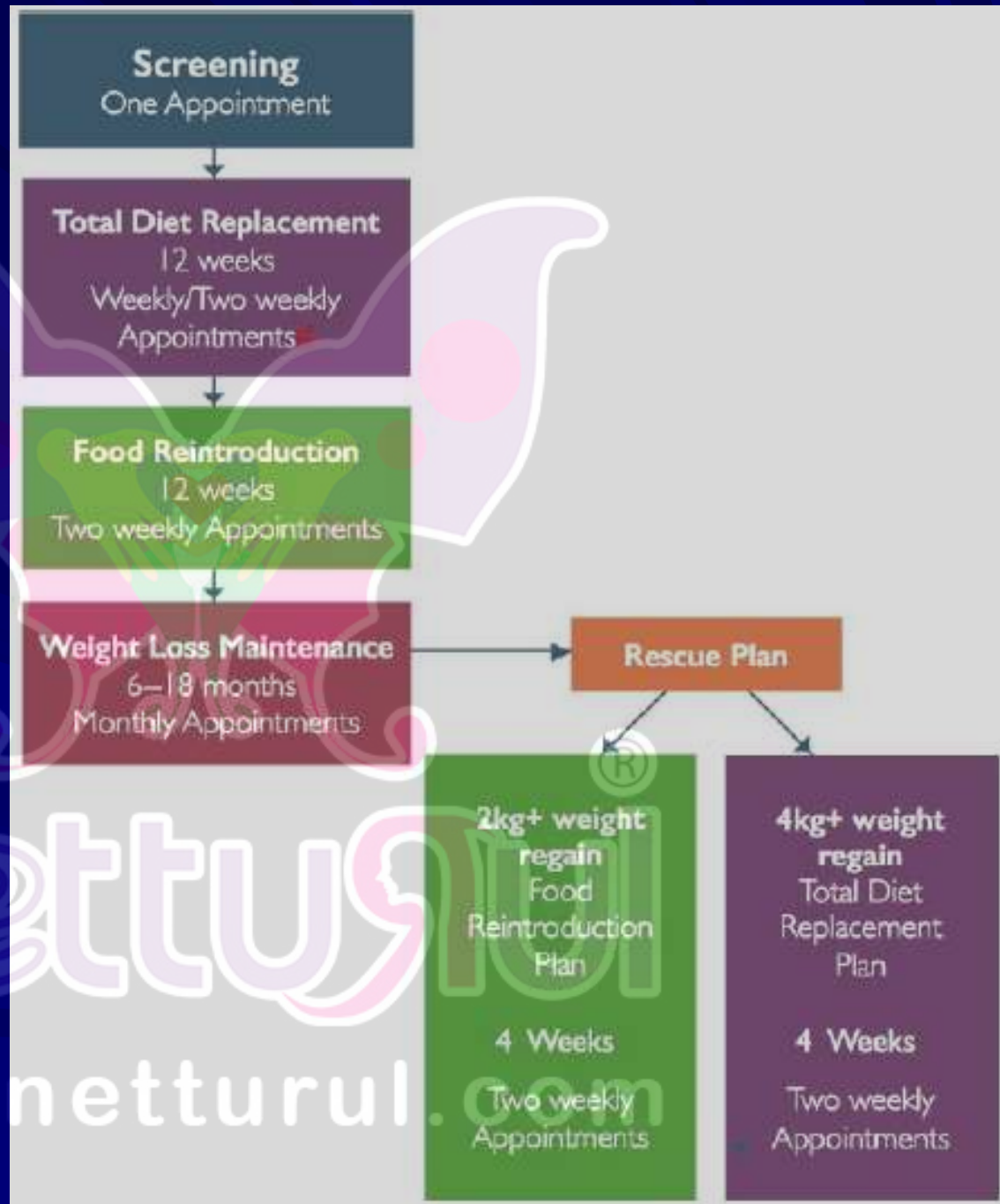
J Hum Nutr Diet 2018

<https://doi.org/10.1111/jhn.126>

11 Nov 2018

n=288

- Average
- Age 47
- Weight 128kg
- BMI 46
- n with T2DM 99



McCombie L et al Filling the intervention gap: service evaluation of an intensive nonsurgical weight management programme for severe and complex obesity.

J Hum Nutr Diet 2018 <https://doi.org/10.1111/jhn.12611> Nov 2018

Proportion of completers in each Weight change group

Weight change kg	3 months %	6 months %	12 months %	24 months %
Gain	1	2	2	20
0 - <5	11	6	18	9
>5	87	93	79	72
>10	61	69	57	57
>15	33	48	22	39
n	277	246	217	46

n = number of completers at each time point

KEY MESSAGE: >10kg weight loss can be maintained up two years in ~60% of completers in a routine setting

Christensen P, Larsen TL, Westerterp-Plantenga M et al 2018 Men and women respond differently to rapid weight loss: Metabolic outcomes of a multi-centre intervention study after a low-energy diet in 2500 overweight, individuals with pre-diabetes (PREVIEW)

Diabetes Obes. Metab. <https://doi.org/10.1111/dom.13466>

Frequency of adverse events

Probability of adverse events

	all	women	men	all	women	men
number	2224	1504	720	2224	1504	720
%	%	%	%			
Constipation	7.6	8.6	5.6	1 in 13	1 in 12	1 in 18
Muscle weakness	5.0	5.1	5.0	1 in 20	1 in 20	1 in 20
Headache	3.0	3.7	1.4	1 in 34	1 in 27	1 in 72
Dizziness	2.0	1.8	2.4	1 in 51	1 in 56	1 in 42
Diarrhoea	1.5	1.7	1.1	1 in 65	1 in 58	1 in 90
Dry skin	1.0	1.1	0.8	1 in 97	1 in 88	1 in 120
Hair loss	0.9	1.2	0.1	1 in 117	1 in 84	1 in 720
Gout	0.3	0	0.8	1 in 371	<1 in 1504	1 in 120