A painting of a mountain landscape. In the foreground, a calm blue lake reflects the sky. A dense line of green trees borders the lake. In the middle ground, rolling hills in shades of brown and green lead up to a large, craggy mountain peak. The sky is filled with soft, white and light blue clouds. The overall style is impressionistic with visible brushstrokes.

**An update on development of guidelines
for diabetes remission - *remission possible!***

Professor Mike Lean

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University of Glasgow

LIBRARY



- **Disclosures:**
Departmental research funds, support for conference attendance and fees for advisory boards and lecturing from Novo Nordisk, Lilly, Roche and Sanofi
- Nestle and Oviva. DiRECT is funded by Diabetes UK, with support in kind from Counterweight Ltd.
- DiRECT slides are posted on:
www.directclinicaltrial.org.uk

How serious is T2D?

How valuable is remission?

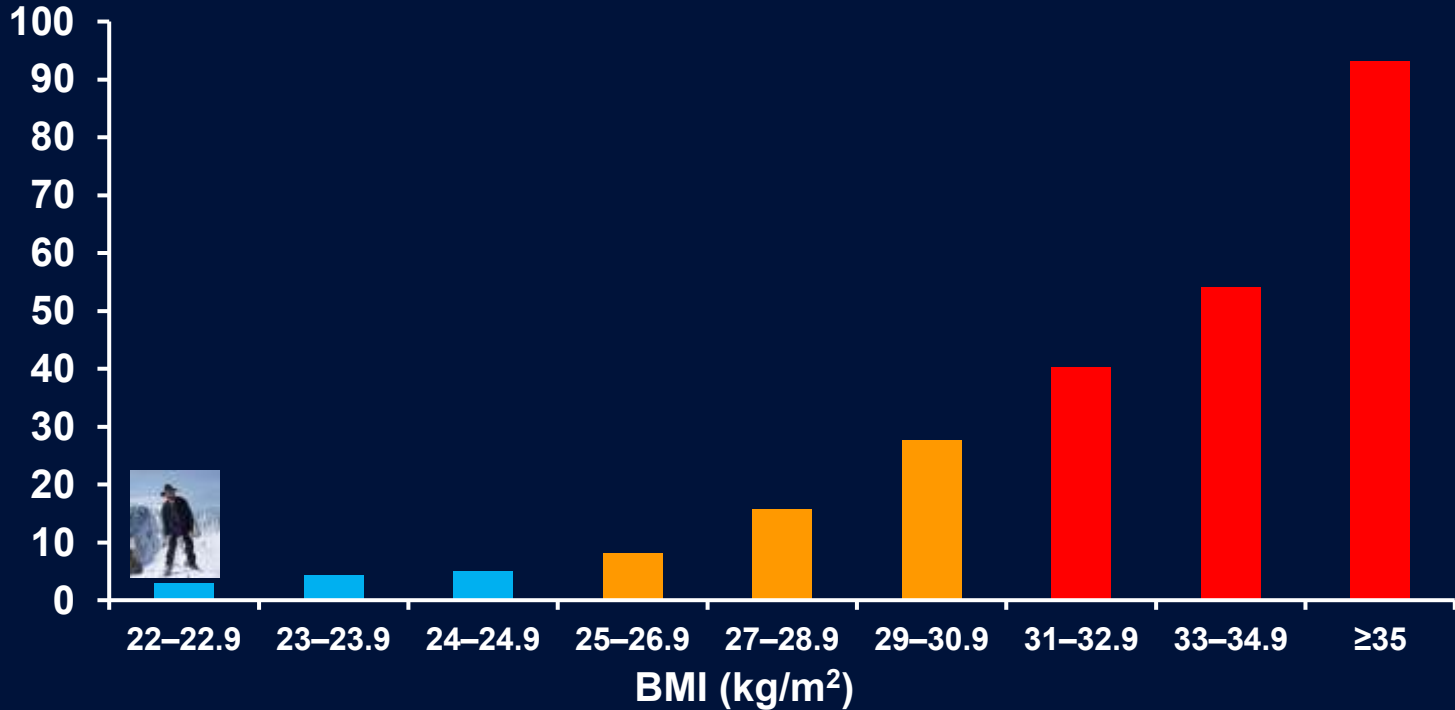
	10-year survival
• Breast cancer	80%
• Non-Hodgkins Lymphoma	60%
• Type 2 diabetes	50%

CRUK website 2021,

Eliasson M et al. Improved survival in both men and women with diabetes between 1980 and 2004- a cohort study in Sweden. Cardiovasc Diabetol. 2008 Oct 20;7:32.

Weight gain/obesity is the main driver of T2D

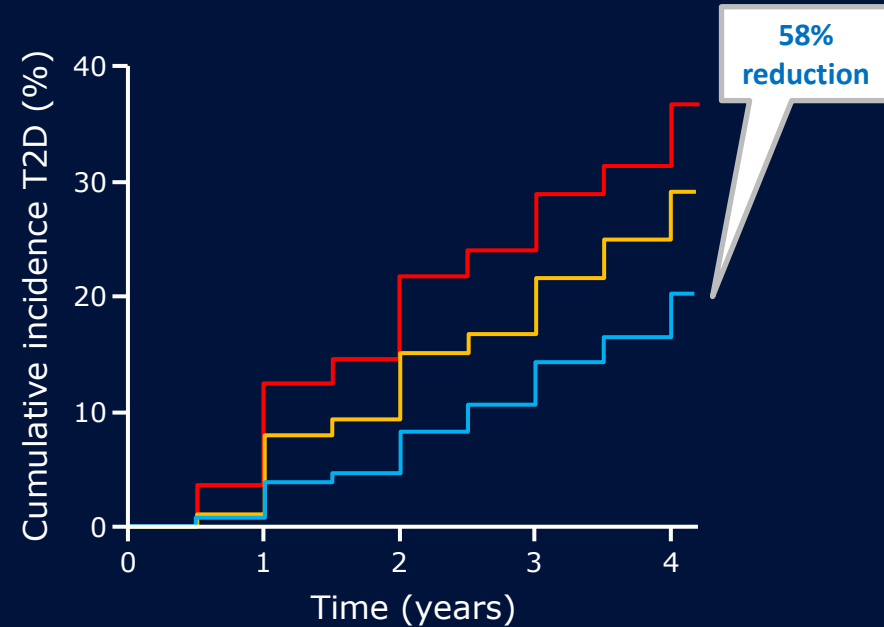
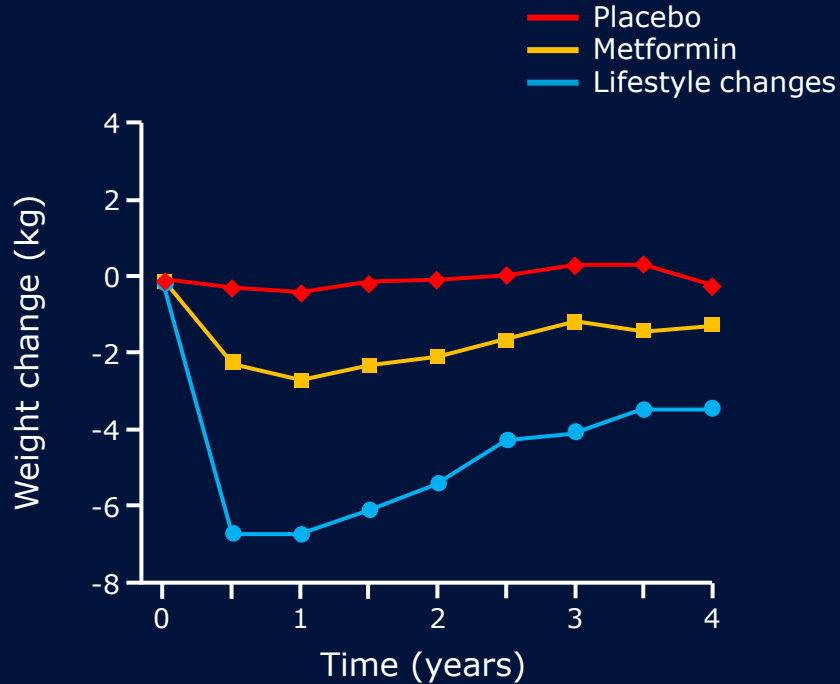
Age-adjusted
relative risk
of developing
T2DM vs.
BMI <22 kg/m²



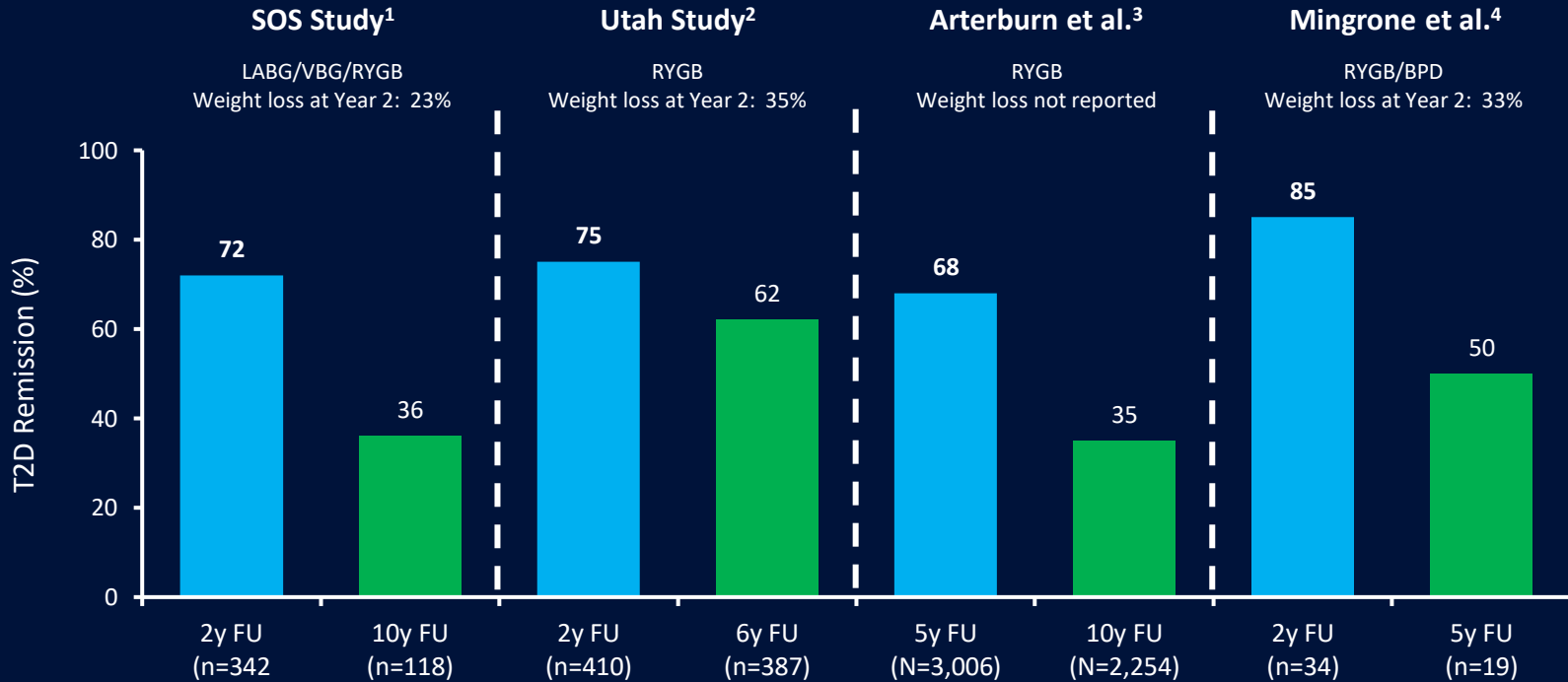
n=114,281 female registered nurses aged 30–55 years
Colditz GA et al. *Ann Int Med* 1995;122(7):481–6

Weight gain, above BMI 23, is the main driver of T2D

DPP, DPS et al: Modest weight loss, early on, prevents most T2D from prediabetes

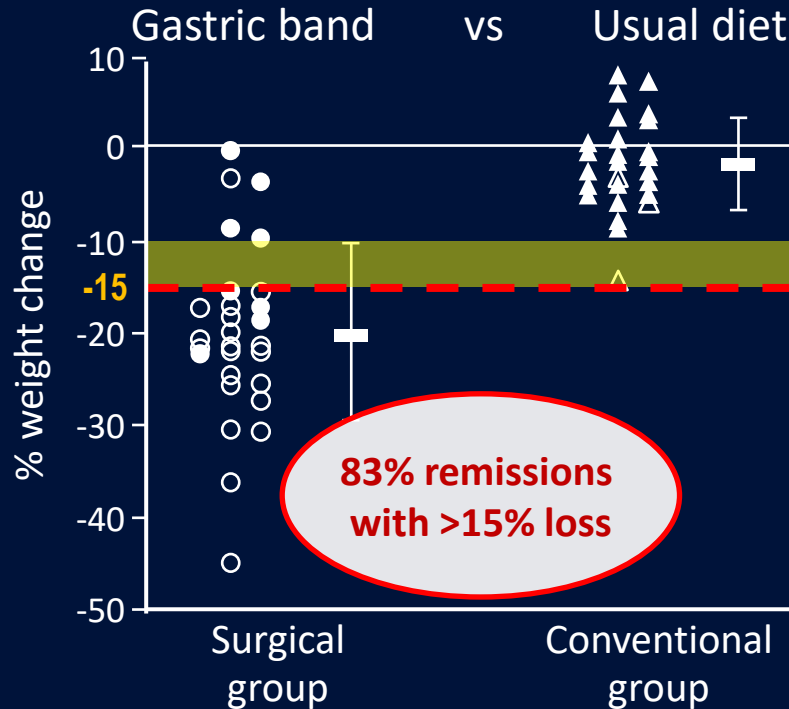


T2D remission after bariatric surgery



BPD, biliopancreatic diversion; EHR, electronic health records; FU, follow-up; LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; SOS, Swedish Obese Subjects; T2D, type 2 diabetes; VBG, vertical-banded gastroplasty
 1. Sjöström et al. N Engl J Med 2004;351:2683–93; 2. Adams et al. JAMA 2012;308:1122–31; 3. Arterburn et al. Obes Surg 2013;23:93–102; 4. Mingrone et al. Lancet. 2015;386:964–73

>10-15% (= >10-15 kg) weight loss achieves most T2D remissions



Conventional group
 Δ Achieved T2DM remission **13%**
 ▲ Did not achieve remission

Surgical group
 ○ Achieved T2DM remission **73%**
 ● Did not achieve remission

DiRECT: Counterweight-Plus diet programme vs Guideline standard care Control group

Practice nurse/dietitian programme delivery

**Withdraw all
anti-diabetic and
anti-hypertensive
medications**

Baseline:

Simple protocol to
reintroduce drugs
if needed



**Total Diet
Replacement
830 kcal/day**

~ 12 weeks

2 weekly
appointments



**Food
reintroduction**

~ 2 months

2 weekly
appointments



**Weight loss
maintenance**

to 24 months

1-2 monthly
appointments

DiRECT/Counterweight-Plus intervention



1. Total Diet Replacement ('12 weeks')

Nutritionally complete (vitamins & minerals)
830 kcal: 61%E carb, 13% fat, 26% protein



2. Stepped Food Reintroduction

Add a ~400kcal meal every 2-3 weeks
Step-counters: gradually increase PA

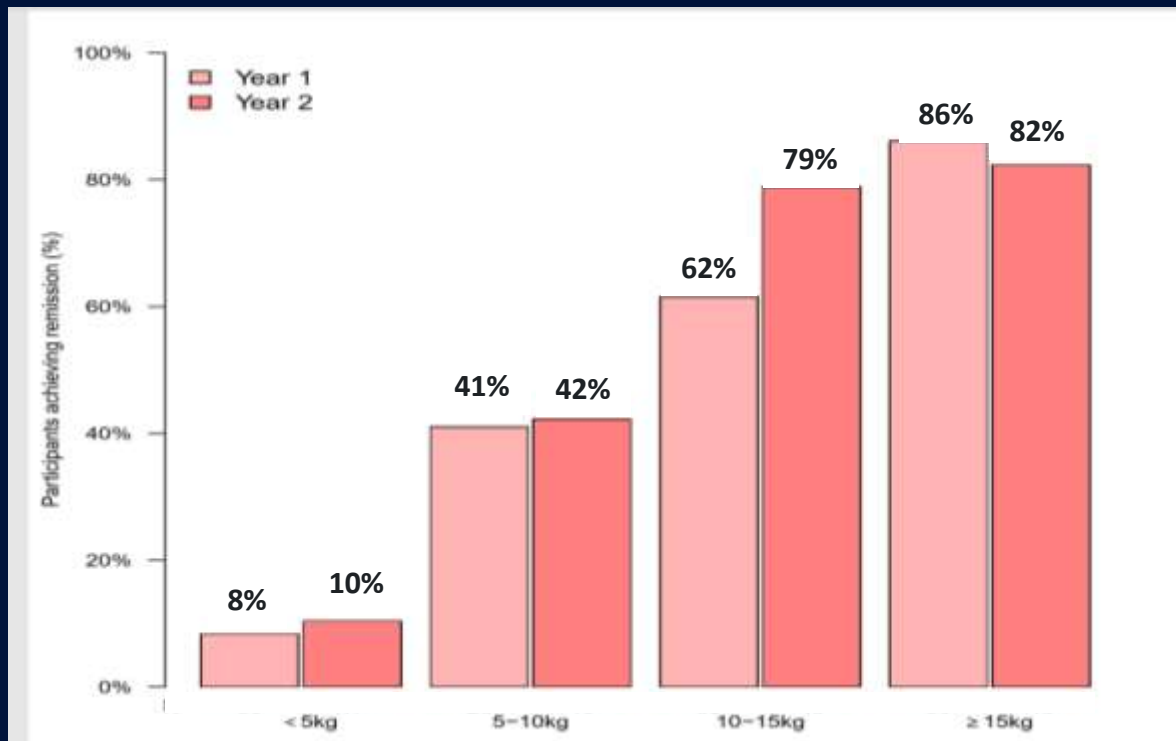


3. Weight Loss Maintenance

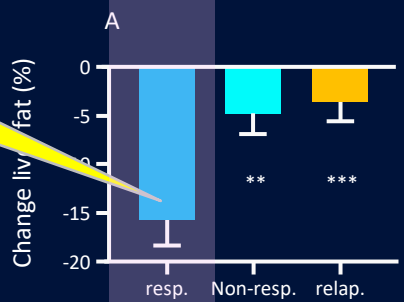
Food-based diet +/- meal replacements
50%E carbohydrate, 35% fat, 15% protein
Offer Relapse Management (regain >2kg)

Visits 2-4 weekly, at own primary care centres
Programme delivered by usual primary care staff

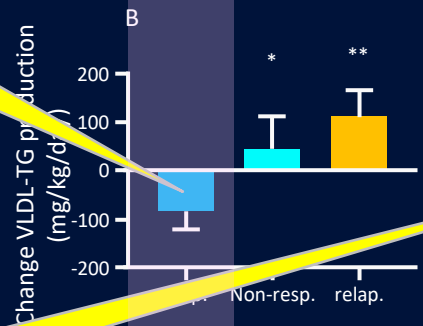
Remissions are well sustained for a given weight change (Intervention Group)



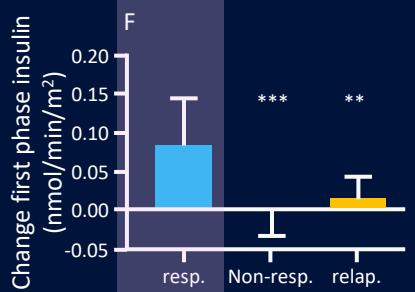
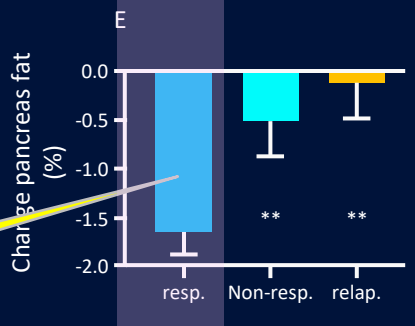
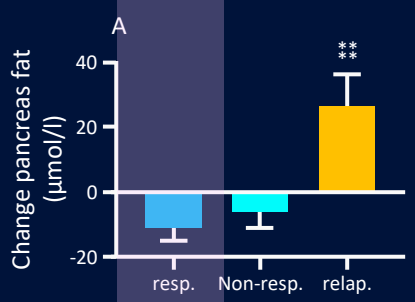
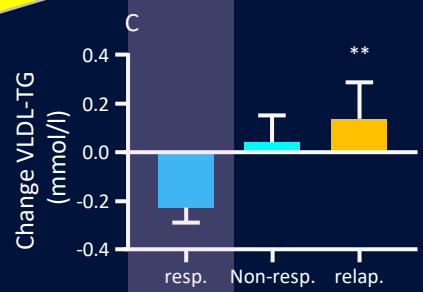
Liver fat falls



VLDL falls



Pancreas fat falls



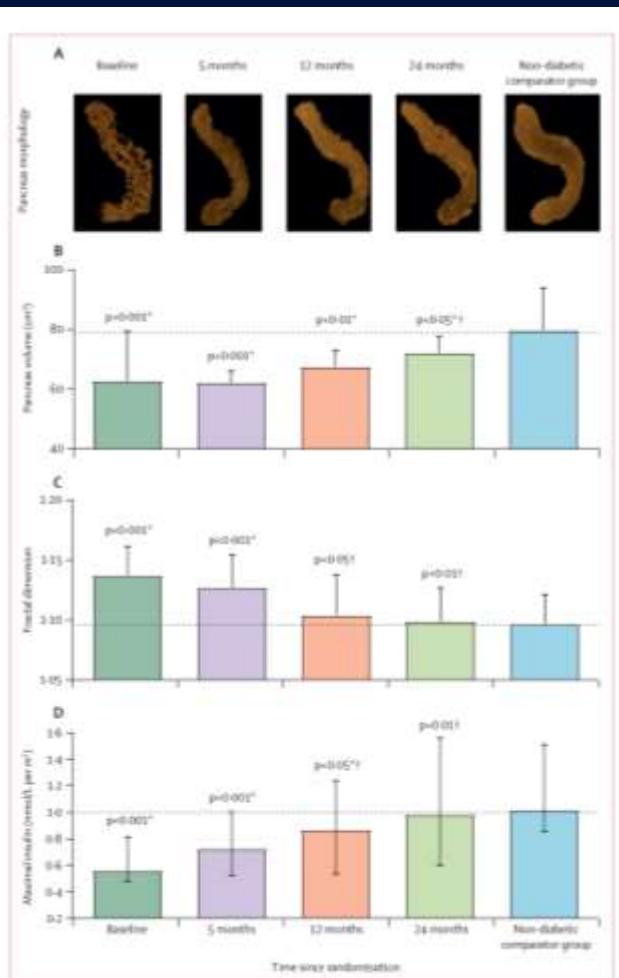
DiRECT: Loss of ectopic fat with remissions at 24 months

Responders (n=20)
Non-responders (n=13)
Relapsers (n=13)

Al-Mrabeh, Lean, Taylor et al
Cell Metab 2019

Remission of T2D is associated with return to normal pancreas morphology and β -cell capacity

Al-Mrabeh et al. Lancet DE, 2020



Pancreas volume

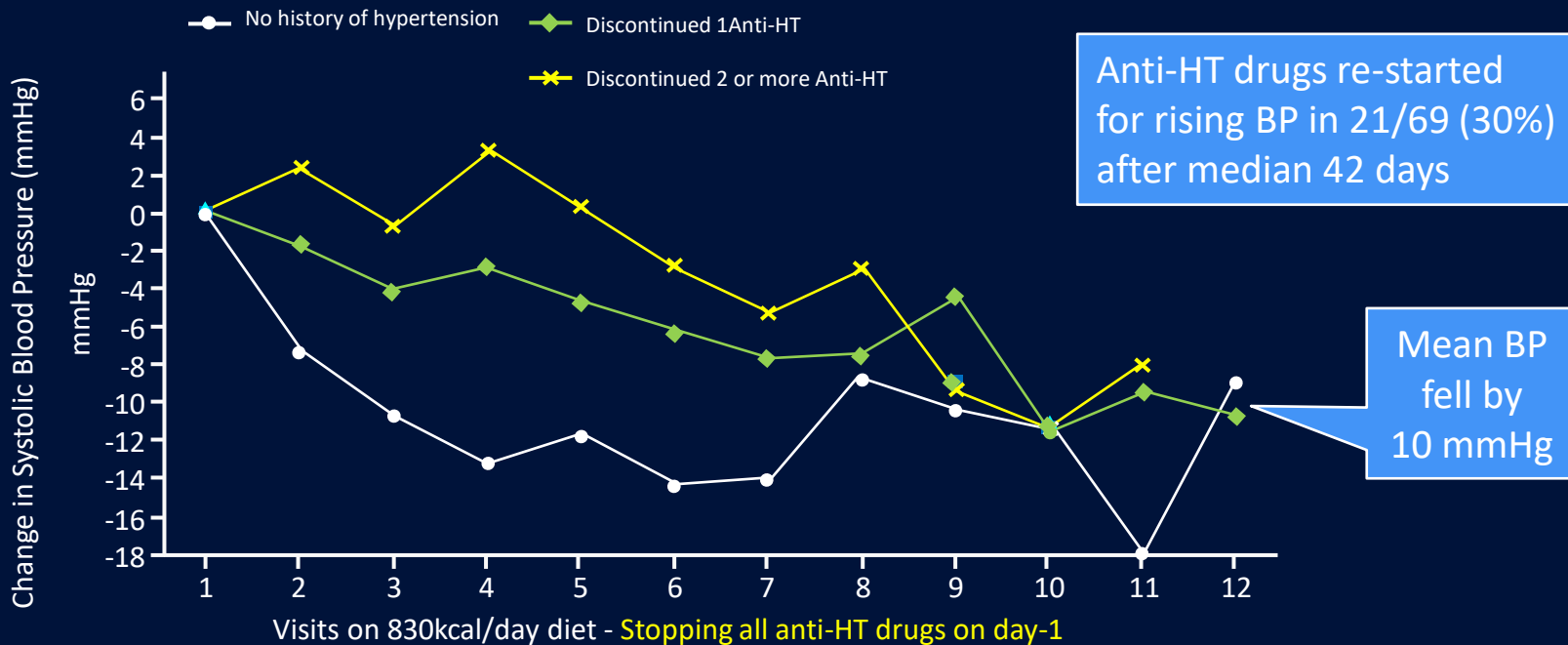
Pancreas raggedness

Max insulin secretion

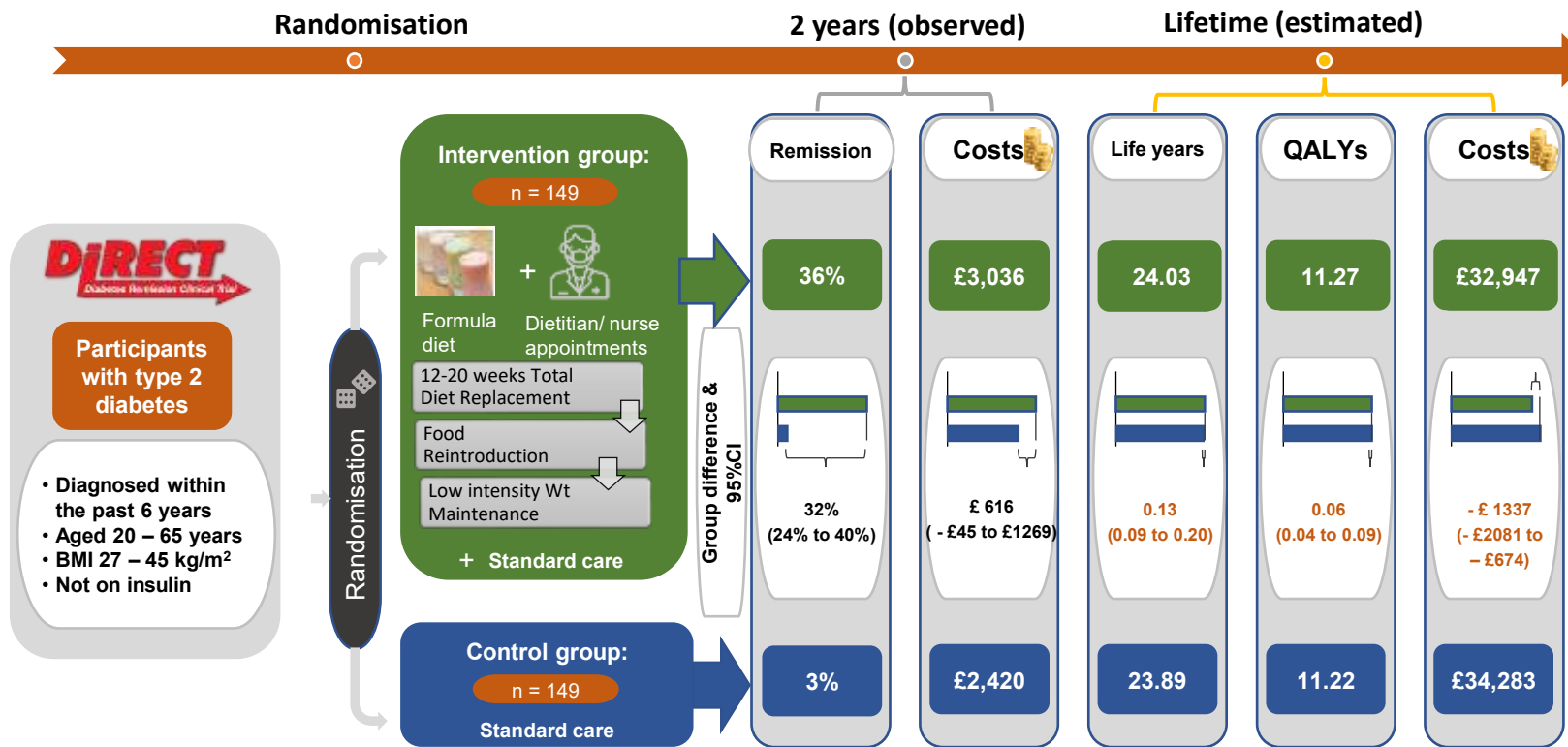
Dashed blue lines = non-diabetic controls

Figure 3: Extent of return to normal among responders over 24 months of pancreas morphology and β -cell capacity

Prevention of postural hypotension and better BP

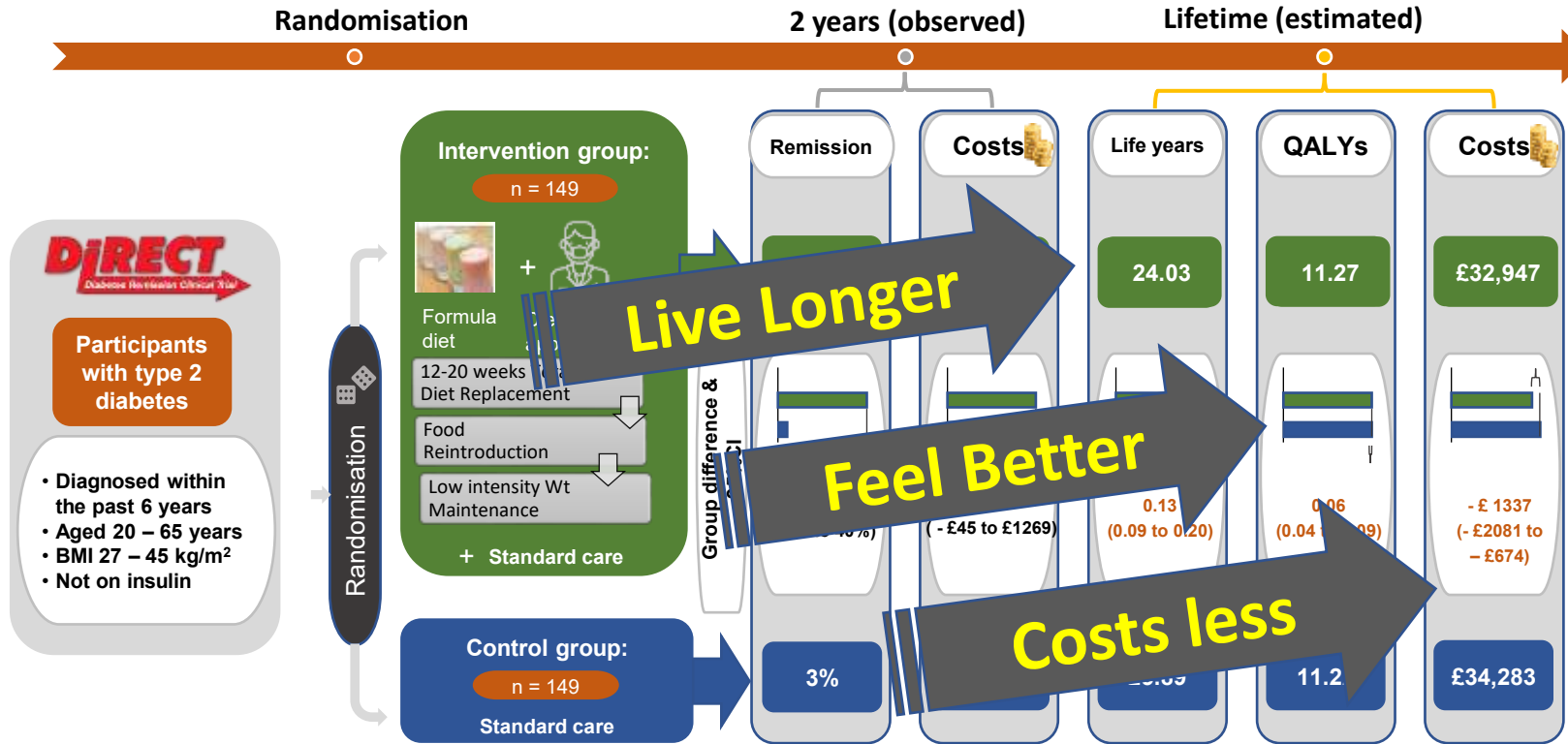


DiRECT Cost effectiveness: Xin, Davies, Briggs, Leslie, McCombie, Taylor, Lean: Diabetologia 2020



The DiRECT/Counterweight-Plus intervention is predicted to be both more effective (QALY gain) and also cost-saving, compared with standard care

DiRECT Cost effectiveness: Xin, Davies, Briggs, Leslie, McCombie, Taylor, Lean: Diabetologia 2020



The DiRECT/Counterweight-Plus intervention is predicted to be both more effective (QALY gain) and also cost-saving, compared with standard care

Criteria for remission of diabetes

1. Level of blood glucose/HbA1c
2. Duration without glucose-lowering medication
 - John Buse ADA statement (2009): HbA1c <42mmol/mol (<6%),
ie. pre-diabetes. No duration specified
 - McCombie et al BMJ 2017: HbA1c <48mmol/mol (6.5%) >3 months
 - ABCD/PCDS (2019): achieve by weight loss, to improve BP & lipids

Internationally agreed criteria: ADA, EASD, Diabetes UK, the Endocrine Society, and the Diabetes Surgery Summit (2021):

- **HbA1c <48mmol/mol (6.5%), >3 months without medication**

Diabetes Care 2021; doi:10.2337/dci21-0034

Diabetologia 2021; doi:10.1007/s00125-021-05542-z

Diabet Med 2021; doi:10.1111/dme.14669

J Clin Endocrinol Metab 2021; doi:10.1210/clinem/dgab585

Importance of remission

- Avoid or delay complications of diabetes
- Self-empowerment
- No need to take medication
- Loss of 'diabetic' stigma
- Normalise costs of life assurance, mortgage, travel insurance

Interventions reporting T2D Remissions

Trials	Design	Sample size (ITT)	Test Diet	12m weight loss (kg)		ITT 12m T2D Remissions (%)	
				Interven- tion	Usual care	Interven- tion	Usual care
DiRECT (UK, 2018)	RCT	Intervention=70 Usual care=77	TDR/ Maintenance	-10.0 ^a	-1.0	46%	4%
DIADEM-I (Qatar, 2020)	RCT	Intervention= 70 Usual care= 77	TDR/ Maintenance	-12.0 ^b	-4.0	61%	12%

TDR, total diet replacement;
Churuangasuk, Halls, Reynolds, Griffin, Combet, Lean. Diabetologia, 2021

Interventions reporting T2D Remissions

Trials	Design	Sample size (ITT)	Test Diet	Mean 12m weight loss (kg)		ITT 12m T2D Remissions (%)	
				Intervention	Usual care	Intervention	Usual care
DiRECT (UK, 2018)	RCT	Intervention=70 Usual care=77	TDR/ Maintenance	-10.0 ^a <i>Lost >10kg</i>	-1.0	46% 73%	4%
DIADEM-I (Qatar, 2020)	RCT	Intervention= 70 Usual care= 77	TDR/ Maintenance	-12.0 ^b	-4.0	61%	12%
Virta Health (USA, 2018)	Non RCT	Intervention=262 Usual care=87	VLCD/Keto	-13.8 ^a	-0.2	19%	-
Unwin (England, 2020)	Practice audit	With T2D = 473 <i>Persisted with diet = 128</i>	VLCD/Keto	-	-	12.5% (23m) 46%	-
Goldenberg (2021)	Systematic review	12m remission: 2 RCTs n=126 12m weight loss: 7 RCTs n=499	Low/VLCD	-0.3 (NS) (vs control)	-	4% (NS) (vs control)	-
Look AHEAD (USA, 2012)	RCT	Intervention=2570 Usual care=2575	Meal replacements	-8.6% ^b	-0.7%	11%	-

TDR = total diet replacement 850kcal/day

Churangasuk, Halls, Reynolds, Griffin, Combet & Lean. Diabetologia, 2021

What lies (DiRECTLY) ahead?

- New Dietary Recommendations from the Diabetes Nutrition Study Group of EASD (June 2022): **GRADE-based**
- 5-year DiRECT results: **COVID-affected, BREXIT-delayed**
 - % maintaining remissions? Clinical outcomes after remission?
- Proteomics analysis: **Patterns of change reflect T2D development**
- Genetic risk score for CHD risk: **Better than clinical prediction**
- NHS England evaluated roll-out of ‘remission’ programmes:
 - **Using various TDR-based programmes, COVID-affected**
- Remissions in South Asians: **Standby trial, Nepal trial**

Clinical Guidelines

- ADA/EASD Guidelines for glycaemic control in T2D (2018)
 - Brief reference to DiRECT, but no guideline for remission
 - No PPI input into this Guideline

Clinical Guidelines for remission

- Some English Health Authorities (TDR –based programmes)
- All Scottish Health Boards (Counterweight-Plus, as in DiRECT)
- National Clinical Guidelines:
 - Diabetes Australia: 'Type 2 Diabetes Remission Position Statement' (2021)
 - New Zealand: Price Waterhouse Report (2021)
 - Others....



What do people living with T2D want?

Diabetes (Type 2) Top 10 Research Priorities

- 1. Can type 2 diabetes be cured or reversed, what is the best way to achieve this, and is there a point beyond which the condition cannot be reversed?**
2. How do we identify people at high risk of type 2 diabetes and help to prevent the condition from developing?
3. What is the best way to encourage people with type 2 diabetes, whoever they are and wherever they live, to self-manage their condition, and how should it be delivered?
4. How do stress and anxiety influence management of type 2 diabetes and does a positive mental wellbeing have an effect?
5. How can people with type 2 diabetes be supported to make lifestyle changes to help them to manage their condition, how effective are these lifestyle changes, and what stops them from working?
6. Why does type 2 diabetes get progressively worse over time, what is the most effective way to slow or prevent progression, and how can this be best measured?
7. Should diet and exercise be used as an alternative to drugs for the management of type 2 diabetes, or alongside them?
8. What causes nerve damage in people with type 2 diabetes, who does it affect most, how can we increase awareness of it, and how can it be best prevented and treated?
9. How can psychological or social support be best used to help people with or at risk of type 2 diabetes, and how should this be delivered to account for individual needs?
10. What role do fats, carbohydrates, and proteins have in the management of type 2 diabetes, and are there risks and benefits associated with particular approaches?

Nutritionally complete, traditional food, no-cost, diets for weight loss and remission of T2D



Scotland

The 'No Doubts Diet' (850 kcal/d) for 8-12 weeks

- Porridge, lentil soup x 2, + fruit x 3
- Maintenance: add one full meal



Nepal

- Milk breakfast, dahl bhat x 2 (850kcal/d) for 8 weeks
- Maintenance: portion-control, avoid Western snacks

<https://www.directclinicaltrial.org.uk/Documents/The%20Lean%20Team%20No%20Doubt%20Diet%20plan.pdf>
(No formal evidence, yet)

Thank you!

<http://www.directclinicaltrial.org.uk/>

- GP practices and patients
- Academic & clinical colleagues
- Ethical and R&D committees
- Cambridge Weight Plan
- Counterweight Ltd
- Diabetes UK, and funding donors

